DOES NOT CIRCULATE
UNIVERSITY OF MICHIGAN
MAR 23 1953
MEDICAL LIBRARY

Clinical Medicine

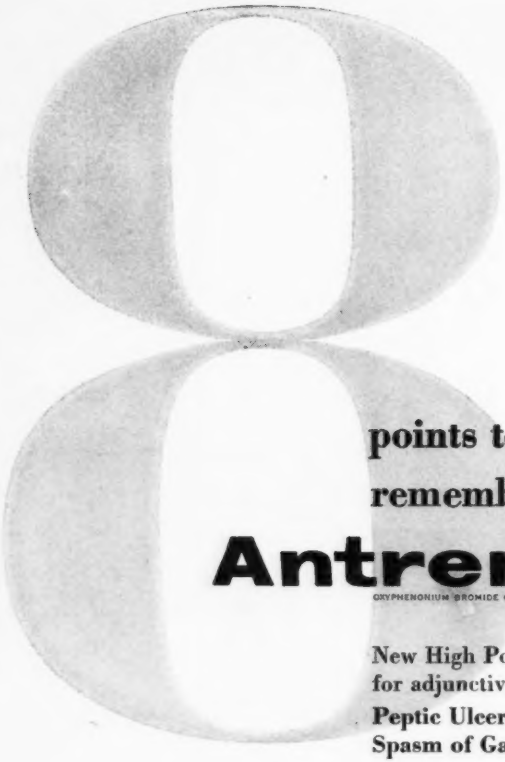
MARCH 1953

University of Michigan
General Library
Ann Arbor, Mich.
0254

General Practice
Peptic Ulcer Therapy
Gamma Globulin
Gouty Arthritis
Juvenile Hypertension
Dysmenorrhea
Cardiac Enlargement
Multiple Carcinomas
Nephritic Edema
Barbiturate Poisoning

Therapeutic Trends
Aids in Diagnosis
New Pharmaceutical Products
Case Report

VOLUME 60, NUMBER 3



points to remember about

Antrenyl™ bromide

OXYPHENONIUM BROMIDE CIBA

New High Potency Anticholinergic for adjunctive therapy in

Peptic Ulcer
Spasm of Gastrointestinal Tract

1. Mg. per mg., one of the most potent of all anticholinergic agents.
2. Recommended dosage approximately *one-tenth* that of certain other anticholinergics.
3. No bitter aftertaste.
4. In individual doses, well tolerated and side effects absent or generally mild.
5. Usually no esophageal or gastric irritation.
6. Convenient q.i.d. dosage schedule.
7. Economical.
8. Two easy-to-take forms: *Tablets* and *Syrup*.

Supplied:
TABLETS, 5 mg., scored; bottles of 100.
SYRUP, 5 mg. per teaspoonful (4 cc.); bottles of 1 pint.

CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

Ciba

TABLE of CONTENTS

60th year of publication

Vol. 60, No. 3 March, 1953

EDITORIAL

Criticisms of the General Practitioner 119
Paul Williamson, M.D.

ORIGINAL ARTICLES

Use of Present Day Drugs in Peptic Ulcer Therapy . . 123
Nathan Steinberg, M.D.

Gamma Globulin: Its Use in Children 131
Carl Weihl, M.D.

Modern Concepts of Gouty Arthritis 134
Robert C. Painter, M.D.

Juvenile Hypertension 144
A. Kappert, M.D.

Some Notes on Dysmenorrhea 147
W. E. Lockhardt, M.D.

CASE REPORT: *Multiple Carcinomas* 149

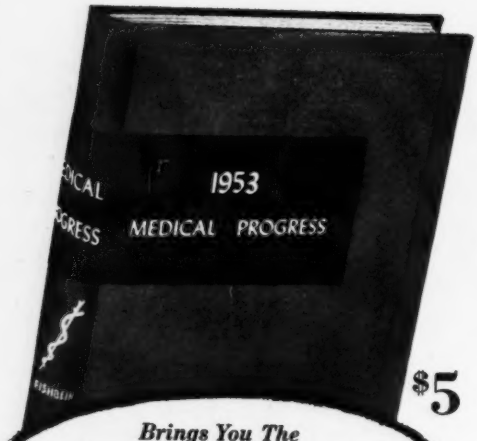
AIDS IN DIAGNOSIS 152

THERAPEUTIC TRENDS 155

NEW PHARMACEUTICAL PRODUCTS 160

Contributions of papers for publication in Clinical Medicine should be addressed to The Editor, Clinical Medicine, Wilmette, Illinois.

Manuscripts should be typed double or triple-spaced, on one side of the paper only. Drawings or photographs will be reproduced at no cost to the author. Bibliographic references should be kept to a minimum. Authors will be furnished reprints at cost. Manuscripts, when accepted, become the property of Clinical Medicine.



Just Published!

1953 MEDICAL PROGRESS

Edited by
Morris Fishbein, M.D.

$5

Brings You The Most RECENT Advances in Diagnosis, Treatment, Trends, Research

Written by 25 of the mo distinguished men in medicine today

Here, in one handsome volume, are gathered together the newest techniques, the vast clinical and research experiences, of such noted specialists as Dr. Paul Dudley White, Dr. Charles W. Mayo, Dr. Frederick W. Stare, Dr. Perrin H. Long and Drs. Irvine H. Page and A. C. Corcoran. For general practitioners, specialists, researchers, and ALL who are interested in the current progress of medicine.

CONTRIBUTORS AND THE CHAPTERS THEY HAVE WRITTEN

1 — ***Cardiology — Heart Disease***
By Paul Dudley White, M.D.

2 — ***Surgery***
By Charles W. Mayo, M.D., and James O. Fergeson, M.D.

3 — ***Infectious Diseases***
By Perrin H. Long, M.D.

4 — ***Arterial Hypertension***
By Irvine H. Page, M.D., and A. C. Corcoran, M.D.

5 — ***Rheumatic Diseases***
By Edward W. Boland, M.D.

6 — ***Nutrition***
By Frederick W. Stare, M.S., Ph.D., M.D.; Theodore B. Van Itallie, M.D.; George V. Mann, M.D.; Jean Mayer, D.Sc., and William R. Waddell, M.D.

7 — ***New and Important Drugs and Medications***
By Paul L. Wermer, M.D.

8 — ***Dermatology***
By Herbert S. Rattner, M.D.

9 — ***Urology***
By Norris J. Heckel, M.D.

10 — ***Psychiatry and Psychosomatic Medicine***
By Francis J. Braceland, M.D.

11 — ***Obstetrics***
By Ralph A. Reis, M.D.

12 — ***Diseases of the Chest***
By Edwin R. Levine, M.D.

13 — ***Ear, Nose, and Throat***
By Francis L. Lederer, M.D. and Burton J. Soboroff, M.D.

14 — ***Gastrointestinal Disorders***
By Clifford J. Barborka, M.D. (Med.) D.Sc.

15 — ***Allergy***
By Leon Unger, M.D., and Albert H. Unger, M.D.

16 — ***Orthopedic Surgery***
By C. Howard Hatcher, M.D.

17 — ***Summary Notes on Medical Advance***
By Morris Fishbein, M.D.

400 PAGES **HANDSOMELY BOUND** **$5.00**

ORDER HERE →

BLAKISTON
the
MEDICAL AND SCIENCE PUBLISHERS

THE BLAKISTON COMPANY
575 Madison Avenue, New York 22, N.Y.
105 Bond Street, Toronto 2, Canada

Please send me on a 10-day trial basis ..... copies of Fishbein's 1953 MEDICAL PROGRESS.....$5.00
☐ Check or M.O. Enclosed ☐ Charge ☐ Send C.O.D.
Name.....
Address.....
City..... Zone.... State.....

CM-3/53

EDITORIAL

Criticisms of the General Practitioner

PAUL WILLIAMSON, M.D., *General Practice Staff, University of Tennessee, Memphis, Tennessee*

There can be no doubt at all that much of the criticism directed against the general practitioner has some basis in fact. Like most criticism it is, in the main, unjust, unfair and unnecessary. Let us examine some of the criticisms directed at the G. P. by other members of the medical profession.

One of the most common criticisms is that the G. P. handles too many patients to handle them well. That is, of course, quite true and yet the people who make this criticism seldom stop to think of the problems of rural medicine. To those of us who have been in general practice, such a statement seems foolish.

We realize that we see too many patients and that many times we are forced into practicing medicine that is not the best caliber of which we are capable. On the other hand, no one has offered us any way to keep from seeing these patients. There are a certain number of patients ill in our small towns every day. It is impossible for the rural physician to attempt selecting from among these patients the most ill and give them thorough medical care. That, of course, would be an answer to the problem but, in simple language, such a physician would be run out of town in two weeks.

In many rural localities, you can't turn down a case for you are the only one available to take care of it. Getting away from your practice is nearly impossible. In a situation such as this it is unnecessary to tell a man that he sees too many patients to do them justice. Nobody knows it better than he. The answer is not to

criticize but to attempt to find some way to get more nonurban physicians in practice.

Another very frequent complaint is that the country doctor doesn't keep up. It seems to me that that depends upon what you mean by the words "keep up". If you mean is he a master of the current theories on physiology of the ovary, of course, he doesn't. If you mean, does he add as much as possible to his fund of practical medical knowledge, you will find most rural physicians do. Here again you find the nonurban physician caught in an awkward predicament. Until very recently little effort has been devoted to providing him with study material that applies to his practice. Most of our medical journals and much of our post-graduate teaching covers elements of medical practice that, while interesting, are of no service to the active general practitioner. Medical literature is still far too complicated to be of day to day use to the nonurban physician. The average medical editor is on the lookout for articles that "contribute" something to the fund of medical knowledge. Actually they should be on the lookout for articles that simplify and make practical good, usable, daily procedures.

In the past half dozen years there has begun to develop a style of literature designed for general practitioners which, surprisingly enough, shows the best readership figures in all medical literature. That, I think, refutes directly the statement that the general practitioner doesn't keep up. He simply has had nothing provided to help him keep up in the past. His reading time has been so limited that he has not had opportunity to wade through 40 pages to dig out one utilizable fact. His post-graduate time has been of necessity so short that he has had to take the briefest courses wherever he could get them. Until the last ten years, few of these brief courses were available.

Another criticism of the G. P. is that he will try anything and everything. Some physicians certainly do this and I hold no brief for them. On the other hand, I hold no brief for the physician who takes the standpoint that his own particular art is so difficult that nobody else could possibly accomplish it without training identical to his own. Medical education is somewhat to blame for such a situation. A typical situation is this: in medical school a student is told repeatedly that he cannot do this and he cannot do that. He is warned about the extreme dangers of practically every procedure he hears about. This warning has some basis in fact for there is scarcely a procedure in medicine that is not dangerous with a lack of caution. By the time the medical student graduates, he is thoroughly convinced that he can do nothing. In his internship little is done to dispel that notion for he sees most procedures done by second or third year residents with the respectful attention of first year residents and interns expected. Then he gets out into practice.

He is faced with the absolute necessity of doing, for example, an appendectomy. He invades the abdomen and by the time the operation is complete, he is usally a good deal sicker than the patient; yet, the patient does quite well. He tries several more times and finds out that many of the procedures he has been warned against are quite simple. Having no basis at all upon which to make a judgement, he then lets the bars down and tries everything. In many cases, he will discover that his over-all mortality and morbidity

rates are poor compared with those of well trained men.

I lay this mistake directly at the door of those of us in medical education. There are procedures in every field that are well within the pale of the general practitioner, but which young men have been warned not to attempt. This, of course, is false reasoning. By the time our students graduate, they should be able to do an uncomplicated appendectomy and should be able to remove tonsils and adenoids. They should be able to do the simpler procedures in x-ray diagnosis and should be capable of handling the therapy of most any routine disease. It would be indignantly denied by most any medical school that they are not so trained.

The general practitioner is frequently looked upon as somewhat avaricious by the rest of the profession. This, of course, is a beautiful example of the pot calling the kettle black. There are financially unsound men in the ranks of general practice just as there are financially unsound men in the ranks of pediatrics or internal medicine. By and large all practitioners of medicine, whether specialized or general physicians, are not economically minded to the detriment of their patients.

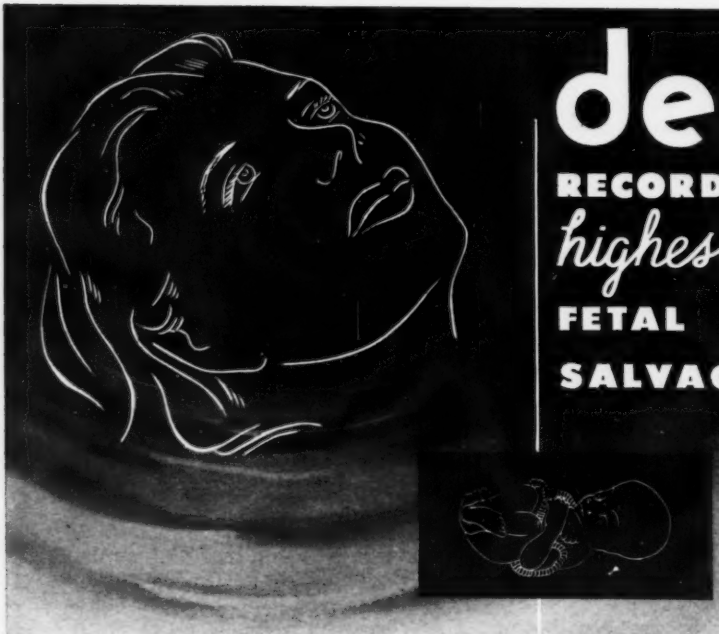
I believe, that few physicians not actively engaged in general practice have realized how tremendously the cost of such a practice has gone up in the past 20 years. All of us can remember the day when the general practitioner needed the simplest of offices, a car, and a well equipped little black bag. Now it is unusual to find a family physician without relatively complete x-ray facilities, without many, many thousands of dollars worth of diagnostic and therapeutic instruments and without an expensive office routine. It certainly does force the general practitioner to charge higher fees than he has charged in the past.

A final complaint which we all hear quite often is that the general practitioner does not refer things soon enough. This statement is quite true in some instances and quite silly in others. You can certainly appreciate that carried to its utmost point, referring things "soon enough" would mean that before long the general practitioner would be simply an expert at deciding which doctor a patient should see.

Any physician, I believe, is justified in watching and treating a disease that does not threaten a life or the physical integrity of the patient until he has proved that it is beyond his ken. An example would be a case of pneumonia that consistently gets worse and shows complications in spite of the best therapeutic efforts of the general physician. There is no difference between three hundred thousand units of penicillin given daily by an internist or by the general practitioner.

It takes two people for a referral. The doctor has to request the patient to go and the patient must be willing to go. Nobody who has not attempted to persuade a cantankerous and doubtful old farmer to go to the city to see a specialist is in a position to say just how difficult this is.

This has been a summary of some of the critical statements made about general practitioners with rebuttal. I certainly want to admit that, being an unreconstructed general practitioner myself, the viewpoint of the G. P. has been stressed throughout. Like most critical statements, those levied against family physicians are more frequently a result of misunderstanding than they are hostility. It is my sincere hope that as the years pass all physicians may understand one another's problems and thereby make them easier to solve.



des

RECORDS *highest* FETAL SALVAGE

With **des** routine, Gitman and Kaplowitz[1] obtained 15 live births from 17 women with histories of one abortion — 88%.

And 3 live births from 3 women with histories of 3 abortions—100%—concluding that **des** is the "drug of choice" in these complications of pregnancy.

Ross[2], with similar **des** routine, brought all of 36 cases of threatened abortion successfully to term 100%. He concluded that "**des**, together with the recommended technique of its administration" is "the method of choice in the treatment of threatened abortion."

Karnaky[3] by the use of massive **des** dosage totalling 30 grams obtained living term infants from a woman who previously had six abortions — and a living infant by using 77 grams of **des** in a woman who had 13 previous abortions.

des 25 milligram tablets — highly micronized, triple crystallized diethylstilbestrol U.S.P. (Grant Process) — dissolve within a few seconds and are uniformly absorbed into the blood stream.

des 25 milligram tablets are available in containers of 30 and 100 tablets.

NOW AVAILABLE

NEW des potencies for massive dosage therapy.

des 50 mg. micronized diethylstilbestrol tablets

des 100 mg. micronized diethylstilbestrol tablets

REFERENCES:

1. Gitman, L., and Kaplowitz A.: Use of diethylstilbestrol in complications of pregnancy. New York State J. Med. 50:2823: 1950.
2. Ross, J.S.: Use of diethylstilbestrol in the treatment of threatened abortion. N. Nat. M.A. 43:20, 1951.
3. Karnaky, K.J.: Am. J. Obsts. & Gynec. 58,622. 1949.

For further information, reprints and samples, write Medical Director

GRANT CHEMICAL COMPANY, INC.

95 MADISON AVENUE, NEW YORK 16, NEW YORK

ORIGINAL ARTICLES

Use of Present Day Drugs in Peptic Ulcer Therapy

Use of the new synthetic anticholinergic drugs in the management of peptic ulcer.

NATHAN STEINBERG, M.D., *Gastroenterological Departments of the Community Hospital, Wolffe Clinic, and Valley Forge Heart Institute, Philadelphia, Pennsylvania*

During the past three decades there has been a decided trend from surgical to medical treatment of peptic ulcer. Zollinger in 1938 reported that the figure of 57 per cent of hospital admissions for peptic ulcer operated on from 1903 to 1926 had dropped to only 7 per cent in the period from 1932 to 1938. Lahey and Marshall in 1943 reported operation in 6.5 per cent of a total of 6,500 cases of duodenal ulcer and 18 per cent of 450 of gastric ulcer. Newer technics, such as vagotomy, either alone or combined with gastrectomy, have not led to an increased use of surgical measures. This is especially true in the more commonly occurring cases of duodenal ulcer, in which resection has not proved as satisfactory as for gastric ulcer. Boles[1] is of the opinion that the possibility of gastrojejunal ulcer presents a formidable objection to resection for duodenal ulcer, and every effort possible should be made to avoid operation in these cases. Toward this end it is felt that a better knowledge of the drugs employed in carrying out adequate medical therapy should prove helpful.

1. Boles, R. S., *J.A.M.A.*, 136:528, 1948.

SYNTHETIC ANTICHOLINERGIC DRUGS

The most recent advance in medical management of peptic ulcer has been the development of the new synthetic anticholinergic drugs, such as Banthine Bromide® (methantheline bromide, Searle), Skopolate (Methyl Scopolamine Nitrate, Strasenburgh), Dibutoline® (Merck), and others. These drugs have an atropine-like action but induce somewhat milder side reactions.

The first of such synthetic drugs and the one to early become widely used is Banthine. Grimson *et al*[2] are of the opinion that Banthine constitutes a medical treatment better than heretofore available and that the need for operation has decreased and will decrease further. While they recommend a dose of 100 mg. every 6 hours day and night. Winkelstein[3] believes that equally good results can be obtained by using 50 mg. doses before meals and at bedtime. It has been our experience that in many cases it would be well to start with 25 mg. doses and then increase the dosage to tolerance or until relief is obtained.

Among the new antispasmodic drugs which I have investigated have been Dibutoline[4] and Skopolate. Dibutoline is effective only hypodermically and its action lasts only 2 or 3 hours. This is of some advantage among patients who have prostatic enlargement, since by advising such patients to urinate prior to each injection, no instance of urinary obstruction has occurred. It has proved especially helpful in those cases of peptic ulcer in which the patient suffered a recurrence complicated by severe pain and nausea. When hospitalization was impossible or refused, application of the Multidose Injector[5] permitted administration of from 0.5 cc. to 1 cc. (25 mg. per cc.) every 3 hours. This usually brought about prompt relief. Lorber[6] found that side reactions following therapeutic doses were similar to those caused by atropine but less intense.

DESCRIPTION OF DRUGS

Skopolate or Methyl Scopolamine Nitrate is a colorless crystalline substance freely soluble in water which has been widely studied during the past number of years by many Swedish and Danish investigators. Scopolamine, by itself, is described by Gruber[7] as a drug possessing properties similar to atropine in that it has both a peripheral and central nerve action. However, scopolamine in its central behavior differs from atropine in that large doses, instead of a delirifacient action, it produces a pronounced depression on the motor and psychic centers of the brain varying from a hypnotic to a narcotic effect. Following a larger dose, the patient usually goes to sleep from five to eight hours. For this purpose it is of value in pneumonia, septicemia and in the presence of a feeble, dilated heart or pronounced circulatory impairment. The peripheral nervous effects of scopolamine are essentially those of atropine inducing depression or paralysis of the terminals of the vagosacral antonomic system and of the secretory nerves.

From past and present studies it appears that the addition of the nitrate radicle has greatly enhanced

2. Grimson, K. S., Lyons, K. C., and Reeves, R. J., *J.A.M.A.* 143:873, 1950.
3. Winkelstein, A., Exhibit at Scientific Assembly, American Medical Association, June, 1951.
4. Steinberg, N., *Rev. Gastroenterol.* 15:319, 1948.
5. Steinberg, N., *G.P.* 2:51, 1950.
6. Lorber, S. H., pp. 34-38, *Postgraduate Gastroenterology*, W. B. Saunders Company, Philadelphia, 1950.
7. Gruber, G. M. Scopolamine (Hyosine) The Cyclopedia of Medicine and Surgery. Vol. 12, pp. 631-636, F. A. Davis Co., Philadelphia, 1952.

the peripheral effect of scopolamine. Using the isolated intestinal strip Methyl Scopolamine Nitrate was found to have five times the anticholinergic effect of atropine sulfate. Like the latter, when administered in moderate doses only the volume of gastric secretion was affected but in larger doses both rate and acidity were also depressed.

Skopolate has greatly reduced the need for surgery in the treatment of pyloric stenosis occurring in infancy. It has been successfully employed in the treatment of peptic ulcer where the usual subcutaneous dose of 0.5 mg. has been found to be six times as potent as the oral dose. In the small number of cases treated by us, the majority obtained immediate relief from their ulcer distress. It proved especially valuable in the presence of severe pain or where other anticholinergic drugs had previously proved without effect. A single injection at bedtime was self administered by one patient to prevent recurring night pain due to a duodenal ulcer. While Dibutoline in 25 mg. doses relieved him for two hours it failed to prevent his being awakened with epigastric pain during sleep.

Skopolate was usually administered hypodermically as a single dose in the office or every eight hours for two to three days or occasionally longer in the hospital. Thereafter it was given orally beginning in one or two milligram doses before meals and bedtime and if necessary increased to three or four milligram doses or to tolerance. In one patient where x-ray and gastroscopy failed to reveal a clinically suggestive ulcer recurrence the subcutaneous administration of Skopolate brought about prompt relief. For the latter reason in doubtful cases this drug, used as a basis for a therapeutic trial, can help confirm or rule out the presence of a peptic ulcer. It is also interesting to note that Wolffe and his associates having been using Skopolate in 1 c.c. doses to aid in the differential diagnosis between the pain of prethrombotic coronary lesions and peptic ulcer It appeared that only patients with non-coronary pain were relieved by this drug.

Prantal Methylsulfate® (diphenmethanil methylsulfate, Schering) has a cholinergic blocking action as shown in its power to inhibit synaptic transmission across certain ganglia in the parasympathetic nervous system of certain animals. Tested in the recommended dose of 100 mg. every 6 hours by Boyer *et al*[8], Prantal was found ineffective in 10 of 11 subjects. It was only when the dose was raised to 500 or 600 mg. that evidence of a selective cholinergic block was noted. While prompt and sustained relief was obtained with such large doses, unpleasant side reactions occurred similar to the other anticholinergic drugs.

Bentyl Hydrocholoride® (dicyclomine hydrochloride, Merrell) has been shown by Hock[9] to be a valuable antispasmodic agent in the treatment of functional disorders of the digestive tract. Miller[10] has used Kolantyl® (combination of Bentyl aluminim hydroxide gel, magnesium oxide, sodium laural sulfate and methylcellulose, Merrell) in the treatment of duodenal ulcer. In comparative studies he claims Kolantyl to be more effective than Banthine. In the relatively few cases studied we found that Kolantyl was effective in an occasional case but in those in which the pain was severe, the more potent antispasmodic, Banthine or Skopolate, was employed.

8. Boyer, A. E., Kemp, P., and Bradford, Sarah, *Gastroenterol.* 22:112, 1952.
9. Hock, C. W., *J.A.M.A.* Georgia 40:22, 1951.
10. Miller, B. N., *J. South Carolina M.A.* 48:, 1952.

UNTOWARD REACTIONS OF ANTICHOLINERGIC DRUGS

More important than learning the therapeutic value of a new drug is knowledge as to its possible side effects. More detailed information as to proper handling of such untoward reactions will enable one to administer with confidence the potent antispasmodics Banthine, Dibutoline and Skopolate. In therapeutic doses all these drugs induce either dryness of the mouth or blurring of near vision, or both. If the patients are so informed and as long as the pain is relieved, there is not too much objection to this inconvenience. Fortunately, the patient can also be informed that the side effects are temporary and cease soon after administration of the drug is stopped.

For example, when Banthine caused acute glaucoma in two patients at the Valley Forge Heart Institute, the application of eserine in the form of eye drops brought about complete relief. These two patients were in their early forties and the ophthalmologist urged immediate iridectomy. However, our previous experience made us decide against such radical measures. Thereafter, we palpated the eyeball of patients in the older age groups and gave smaller doses in order to determine the patient's tolerance.

When a draftsman suffering from irritable colon developed marked blurring of vision after taking only 50 mg. of Banthine, we realized that patients who do close work cannot take this drug while employed. In such cases we first attempted the employment of the less active antispasmodic drugs such as Prantal, Bentyl or Transentine® (adiphenine hydrochloride, Ciba). While administering Dibutoline in 25 mg. doses every 3 hours to one patient, whose recurrence of duodenal ulcer was complicated by an enlarged prostate, difficulty on urination developed. He was advised to void prior to each injection and thereafter for the three days of therapy suffered little inconvenience.

When ulcer pain and/or vomiting do not respond to anticholinergic therapy it may mean a surgical complication but more often the need for the employment of a more potent drug. Thus, Skopolate, because of its greater potency and prolonged activity, proved effective in the treatment of a patient suffering from a gastric ulcer after other drugs had failed. Here the necessity for infrequent injections and the prompt relief of pain made the accompanying dryness of the mouth and blurring of vision acceptable to the patient. In another patient seen with ulcer pain simulating gall bladder colic, a single injection of 0.5 mg., of Skopolate controlled the marked epigastric distress. Other patients objected to Skopolate because of the extreme and prolonged dryness of the mouth. A reduction of the frequency of administration to every twelve hours lessened such complaints in some cases. It was observed that with an occasional exception Dibutoline induced less intense side reactions than Skopolate. For this reason and since the frequency of administration is of little concern when using the Multidose Injector, Dibutoline was employed in the home and office whenever continuous subcutaneous antispasmodic therapy was indicated. In one case of failure, hospitalization was advised and Skopolate used instead.

Unless the patient was seen in acute distress to lessen the unpleasant side reactions a preliminary dose of a half c.c. of Skopolate (0.5 mg. per c.c.) or Dibutoline (25 mg. per

c.c.) was used as the test anticholinergic drug. If no marked dryness of the mouth occurred fifteen minutes following the injection, the remaining half c.c. was administered. Thereafter, in those patients to be treated at home, Skopolate was given orally in the appropriate dosage determined by the relative severity of the side effects. Banthine was similarly employed by mouth. In elderly patients suffering from prostatic enlargement both drugs have caused urinary retention and should therefore be employed with great caution in such individuals. In one fifty year old male patient Skopolate administered twice daily caused some delay in micturition and constipation. Reduction of the dose to a single injection at bedtime to prevent nocturnal pain lessened this difficulty.

The only untoward cerebral effect observed was occasional dizziness lasting for a few minutes following an injecion of 0.5 mg. of Skopolate. We have not observed the highly excitable or delirious state seen in the obstetrical patient given combined morphine and Scopolamine to control pain during labor.

ANTACIDS

Although excessive secretion of hydrochloric acid for prolonged periods does not in itself tend toward ulcer formation, its control is necessary in the healing of peptic ulcer. The antacids now most popularly used are the aluminum hydrozide gels. The frequent tendency toward constipation with prolonged administration has lead to the combination of aluminum hydroxide with magnesium trisilicate or magma magnesia. In spite of such combinations, constipation can become intolerably annoying to some individuals. For such persons the use of anion exchange resins, appearing under various trade names, may be substituted. These products act by absorbing the hydrochloric acid in the stomach and releasing it in the intestines. Their overall effect is increased by an inhibitory action on pepsin. When the patient does not obtain relief, because these resins possess relatively less antacid power than aluminum hydroxide preparations, Ulmets® (methylcellulose, calcium carbonate, and elm bark, Durst) or Carmethose® (sodium carboxymethylcellulose and magnesium oxide, Ciba) may be tried.

Hardt and Steigmann[11] report a more rapid immediate effect in peptic ulcer with a lesser tendency to recurrence with Mucotin® (combination of gastric mucin, aluminum hydroxide gel, and magnesium trisilicate, Harrower). They employed Mucotin in 125 cases, and in the majority, especially in 20 in which previous "intractable" ulcer symptoms were present, a response was rapid. They stated that their recurrence rate was only from 15 to 18 per cent in 12 to 24 months, respectively. All patients were placed on ambulatory management and given from 2 to 4 Mucotin tablets 1 hour before meals, 1 hour after meals, and at bedtime. In severe cases the drug was given hourly. Antispasmodics and sedatives were administered and the patients were advised against the use of alcoholic beverages, coffee, and smoking.

The end results of these authors are far superior to other investigators whose recurrence rate varied from 30 to 80 per cent among both clinic and private patients. However, one cannot determine from their studies whether the improved antacid preparation or their additional use of antispasmodics and sed-

11. Hardt, L. L. and Steigmann, F., *Am. J. Digest Dis.* 17:195, 1950.

atives was responsible for their excellent results.

In a still later investigation, Steigman and his associates[12] evaluated the many antacids now available. Among these were the alkali substances (magnesium hydroxide and Sippy powder No. 1), cellulose substances (Ulmets and Carmethose plus magnesium oxide), colloidal aluminum hydroxide gels, amino-acid combinations, plant mucins (okra), resinous substances and duodenal tissue extracts. Nearly all proved excellent neutralizers of acids, but as yet they report the ideal antacid has not been discovered. It is apparent, therefore, that the antacid must be tailored to each individual patient, taking into consideration taste, tendency to develop constipation or diarrhea, possible alkalosis after prolonged use, renal stones, and acid rebound. Presence of these factors will, in turn, depend to some extent on the age of the patient, history of previous bowel behavior, and status of rental function. Should it be decided to use a mixed preparation (antacid plus sedative and/or antispasmodic), it would seem best to choose an antacid combined only with a sedative because of the marked variability in individual tolerance to anticholinergic drugs.

SEDATIVES

Accompanying the increased irritability of the gastric walls, believed due to the excessive formation of acetylcholine, there is also marked central excitability of the vagal nucleus.[13] To control the vagal center and provide general mental relaxation, the barbituric derivatives have proved best. In some cases the use of phenobarbital in adequate doses, usually ½ gr. four times daily, has proved the equal of any other drug employed in peptic ulcer therapy. If the patient's sleep is disturbed, administration of seconal or pentobarbital at bedtime may be necessary. Of most help is to advise the patient to go to bed soon after dinner for additional rest during the stage of healing. Also, it is well to obtain the family's cooperation in not troubling the patient with minor domestic problems in order to provide for greater mental relaxation and thus lessen the need for sedation. However, for patients employed on swing shifts or working irregular hours among whom antispasmodic drugs had to be employed indefinitely, continuous sedation was also found necessary.

THERAPY OF DUODENAL ULCER IN THE ACUTE STAGE

The majority of ulcer patients desire ambulatory therapy so that they may continue with their daily duties. While it has been shown by Dick and Eisele[14] that in many cases merely placing the patient in bed on a strict Sippy diet will bring about relief of ulcer pain, this does not hold true in the case of the patient continuing at work. When an ulcer patient is seen at home writhing with severe pain, nauseated and attempting to vomit, more radical measures than a Sippy diet are necessary.

It is in these cases that the use of Dibutoline has proved so satisfactory. If the patient can be moved to a hospital or another person is available to administer drugs hypodermically, the injection of from 10 to 25 mg. of Dibutoline every 2 or 3 hours will usually bring about speedy relief. Where hospitalization is for any reason impossible or

12. Steigmann, F. *et. al*, *Am. J. Digest Dis.* 19:310, 1952.
13. Winkelstein, A. and Hess, M., *Gastroenterol.* 11:326, 1948.
14. Dick, G. F. and Eisele, C. W., *J.A.M.A.* 118:38, 1942.

trained nursing personnel is lacking, application of the Multidose Injector filled with Dibutoline will bring about equally good results. The additional time and effort spent by the physician will be amply repaid by the excellent results obtained. The next day the patient will usually be found sitting up, with complete relief of his former epigastric distress.

Before Dibutoline became available, 1/100 gr. of atropine, with or without ¼ gr. of codeine phosphate, was administered every 4 hours, by means of this device. However, when acute urinary retention occurred following the use of atropine in a patient with an enlarged prostate, Dibutoline was substituted.*

Following the use of Dibutoline for 2 to 3 days, the patient is placed on a schedule of 1 mg. of Methyl Scopolamine Nitrate with advice to increase the dose up to 4 mg. or until evidence of tolerance, as indicated by dryness of the mouth or blurring of near vision, occurs. Skopolate (oral) is administered at set intervals as previously recommended. In a number of cases, Banthine was used instead and proved equally effective. Simultaneously with the administration of anticholinergic drugs, the patient was given appropriate antacids, sedatives and a multivitamin capsule containing ascorbic acid. A chart containing three graduated diets, beginning with the Sippy diet, were given the patient to follow in sequence as the symptoms lessened. From one to four teaspoonfuls of a soybean hydrolysate, Protolan, was added to the hourly milk and cream feedings in order to increase the protein intake. If occasionally the taste proved objectionable, whole milk powder was used instead of Protolan.

Alcoholic and caffeine-containing beverages were barred but in spite of advice to the contrary, many continued to use tobacco, although in reduced quantities. It was quickly found that worry, fatigue, anxiety about conditions on the job or in the home, and change of seasons were more often precipitating factors in the recurrence of peptic ulcer than failure to take medication or dietary indiscretions. This was explained to the patient and his family and cooperation to control some of these factors was requested. In some patients continued use of drugs and diet was necessary, in others only for six to twelve months. Still others took medication only for a few weeks and yet suffered no recurrence. However, all ulcer patients must be taught to "live with their ulcers" in order to reduce the great tendency towards recurrence.

Administration of Skopolate or Banthine is usually stopped after two or three months but the patient is continued on antacids and sedatives for one year. At the slightest recurrence of pain the patient is advised to again take this drug and to obtain medical advice.

GASTRIC ULCER

In the treatment of duodenal ulcer the physician can assure the patient that carcinoma is not present and that none will ever develop at the ulcer site. No similar assurance can be given the patient suffering from gastric ulcer. If the ulcer occurs on the greater curvature of the stomach, immediate operation is neces-

*Some physicians may fear breakage of the needle beneath the skin while employing the Multidose Injector. This has never occurred with the present technic, since the rubber tubing limits penetration of the needle to not more than ¼ inch beneath the skin. Breakage, when it does occasionally occur, takes place at the weakest point of a hypodermic needle, namely, the junction of the needle hub and metal tubing. The addition of a thick plastic guard prevents breakage of the glass syringe should the patient happen to fall. All these precautions make it safe to employ the Multidose Injector to administer Dibutoline, since locally this drug has proved to be nonirritating.

sary. If, however, the ulcer occurs on the lesser curvature and there is no definite decision after roentgenoscopic or gastroscopic examination that the lesion is malignant, a therapeutic trial is indicated. To hasten healing, treatment in the hospital is preferred and should include a few days therapy with Dibutoline or Skopolate administered subcutaneously, followed by Banthine or Skopolate (oral), milk and cream with protein hydrolysate, and bed rest. If the ulcer crater does not show marked reduction in size or complete disappearance at the end of two weeks, gastrectomy should be performed.

If hospitalization is refused the Multidose Injector may be employed to carry out parenteral therapy for the first few days. One middle-aged woman with a large pentrating gastric ulcer on the lesser curvature, suspicious of neoplasm, refused to submit to operation. The administration of Protolan mixed with milk and cream plus hypodermic administration of 1/100 gr. of atropine every 4 hours, relieved the pain and vomiting, followed by complete recovery.

SUMMARY AND CONCLUSIONS

1. The status of a patient suffering an acute attack of peptic ulcer is often similar to a patient in the throes of an acute attack of asthma. The patient desires and should be granted relief of distress as soon as possible. Banthine, Dibutoline, and Skopolate (hypodermically and oral) enable this object to be accomplished in the shortest possible time. Failure of these drugs may be attributable to the fact that a practical limit to the dose necessary for relief has been reached, a more powerful anticholinergic preparation is needed, or that a complication has occurred. In such cases, complete bed rest and frequent protein hydrolysate feedings plus hypodermic administration of Skopolate or Dibutoline can often save the patient from surgical intervention.

2. In the hospital, tincture of belladonna, administered in drop doses and gradually increased until tolerance is reached, is an effective and economical drug. However, the inconvenience of taking medicinal drops at work, the time necessary for the drug to take effect, and the occasional failure to bring about relief make the newer anticholinergic preparations the drugs of choice, if cost is not too great a factor, among ambulatory patients.

3. Since Banthine, Dibutoline, Skopolate and other drugs chiefly act to relieve distress by reducing gastric motility, an active ulcer crater can continue in the absence of pain. For this reason, it is necessary to employ antacids and sedatives and to stress the need for the ulcer patient to follow a strict diet, obtain more rest and to avoid coffee, alcohol, and smoking. The less active antispasmodic dugs, such as Prantal and Bentyl in recommended doses, although helpful in functional gastrointestinal disorders, usually were not successful in the control of pain of the ambulatory ulcer patient.

4. For the satisfactory control of intractable nocturnal pain when conventional measures fail, the patient can be taught to self administer Dibutoline or Skopolate at bedtime.

5. Toxic side effects following the administration of Banthine, Dibutoline and Skopolate appeared to be less among patients suffering severe pain. Simultaneously, it was found they could tolerate larger doses of these drugs. By employing small doses at the onset, especially among ambulatory patients, side effects rarely proved troublesome.

Gamma Globulin: Its Use in Children

Inaications for and administration of widely publicized gamma globulin are presented in outline form

CARL WEIHL, M.D., *Cincinnati, Ohio*

I. What is Gamma Globulin:

Gamma globulin is that part of the serum protein which has been shown to contain a large portion of the circulating antibodies against foreign protein antigens. The development of effective physicochemical technics for fractionation of the plasma proteins, combined with the nationwide blood procurement program of the American Red Cross, has resulted in the production of concentrated solutions of gamma globulin, with an antibody activity approximately 25 times that of normal plasma.

The pooling of adult plasma from many donors results in a fairly uniform titre of antibodies in the gamma globulin prepared from the plasma, irrespective of the part of the country in which the blood is collected.

II. When is Gamma Globulin Indicated:

At present there are four definite indications for the administration of gamma globulin:

1. *Measles.* Gamma globulin, the most effective agent yet found for the prophylaxis of measles. may be used either for prevention or modification of the disease. To prevent—0.1 cc/lb. of body-weight, given within 5 days after exposure. To modify (producing attenuated measles)—0.02 cc/lb. of bodyweight, given within 5 days after exposure. After the fifth day, and before the development of prodromal symptoms, 0.1 cc/lb. may attenuate the disease. The duration of protection is about two weeks.

In general, children under 2 years of age and any child already ill with another disease, should receive protecting doses; others may be given modifying doses. (Infants up to 6 months of age already have passive immunity if the mother has had measles.) The immunity following modified measles is probably lasting.

2. *Infectious Hepatitis.* Gamma globulin is very effective, given early in the incubation period, in the prevention of infectious hepatitis. Originally, doses of 0.06 cc/lb. were utilized, but recent studies indicate that, in large institutional outbreaks, doses as small as 0.01 cc/lb. of bodyweight are effective, and that a single dose may confer protection up to 9 months after injection. Gamma globulin should be given to any child intimately exposed to infectious hepatitis as soon after exposure as possible.
3. *Agammaglobulinemia.* Recent studies have uncovered a small group of children who lack circulating gamma globulin and the antibodies usually contained in it. Their ability to resist infections of many types is decreased, and gamma globulin has been a specific therapeutic agent in overcoming infections already present and in preventing the occurrence of new ones. The diagnosis can be established in suspected cases only by an analysis of the serum proteins, demonstrating the presence of a negligible amount of gamma globulin. These children conceivably will have to take gamma globulin injections at periodic intervals, much as the diabetic takes insulin.
4. *Poliomyelitis.* Gamma globulin contains large amounts of antibodies against all 3 immunologic strains of the poliomyelitis virus (Lansing, Brunhilde, Leon). Recent field trials were conducted in 3 epidemic areas during the summer of 1952; in a carefully controlled series of 54,772 children from 1 to 11 years, highly significant protection against paralytic poliomyelitis was demonstrated from the second through the fifth week after injection of gamma globulin; the average dose used was 0.14 cc/lb. (4 cc. up to 34 lb.; 7 cc. from 35 to 61 lbs., and 11 cc. for children 62 lbs. and over).
5. Gamma globulin may exert a definite effect in the prevention of German measles; it certainly should be used whenever a susceptible pregnant woman is exposed to the disease. It is of no value in mumps, either in prevention of the disease or the prevention of orchitis, unless it is specifically prepared from mumps convalescent serum, and given in doses of 20 cc. Gamma globulin may be of some value in the prevention of serum hepatitis, but in no way approximates its usefulness against infectious hepatitis.

III. How is Gamma Globulin Administered:

Gamma globulin should only be used *intramuscularly*; as currently produced, it may produce serious reactions if given intravenously. After intramuscular administration, occasional reactions occur: these may be local (soreness, swelling) or general (fever; rarely urticaria). The solution is viscid, requiring an 18-20 gauge needle for easy administration. It is stable at room or icebox temperatures for as long as 9 months.

IV. Where to Obtain Gamma Globulin:

The American Red Cross processes and distributes gamma globulin, in 2 cc. vials, *free of charge*, the local distribution usually being handled through state or local board of health.

Commercial manufacturers also produce a similar product, available through local druggists, drug supply houses, or biological houses, usually in 2 cc. or 10 cc. vials.

The total supplies of gamma globulin are not nearly great enough to provide protection from paralytic poliomyelitis this summer for all of the nation's children. The National Foundation for Infantile Paralysis and the American Red Cross are combining to obtain as much gamma globulin as possible for use in epidemic areas; this combined supply will be distributed through designated government public health agencies. (The American Red Cross will produce the maximum amount possible from blood donated through the blood centers; the National Foundation for Infantile Paralysis will purchase the limited supplies now in the hands of commercial producers and all that can be produced up to June, 1953.)

Physicians are urged not to use gamma globulin routinely for the prophylaxis of poliomyelitis until the available supply makes it possible to have a surplus above the needs in epidemic areas this summer.

Empiric Low-dosage Irradiation In Amenorrhea

The present study is an analysis of the results obtained over a 15-year period (1936-1950) in 124 patients subjected to x-ray therapy for the treatment of secondary amenorrhea. Excluded from treatment were women with only one ovary or in the condition of pregnancy, and adolescents. The treatment was in the dosage of 50 to 80 roentgen units per week for three consecutive weeks, applied to the pituitary gland and the ovaries.

No obvious relationship was observed between the age of the patients (20 to 35 years) and the response obtained. On the other hand, the severity of the amenorrhea was found to be important, for the rates at which cures were obtained proved to be inverse proportion to the length of the menstrual period or interval. It was also learned in this study that x-ray therapy should be applied only after menstruation has taken place, either spontaneously or by articifial means.

Twenty-seven of the 90 patients upon whom this report is based became pregnant during the course of the year following x-ray therapy, 23 of them giving birth to normal infants at term.

It is concluded that the results obtained lend support to the contention that low-dosage irradiation can be safely employed in properly selected patients with secondary amenorrhea.

(S. L. Israel, *Am. J. Obstr. & Gyne.*, 64:971, 1952.)

Modern Concepts of Gouty Arthritis

A comprehensive presentation of the diagnosis and treatment of one of the oldest known diseases.

ROBERT C. PAINTER, M.D., M.S. (Med.)
Department of Medicine, Grand Forks Clinic, Grand Forks, North Dakota

INTRODUCTION

Gout may be considered as a hereditary metabolic disease and defined as a basic derangement of purine metabolism resulting in an associated "essential" hyperuricemia. Gout is one of the oldest of known diseases. Hippocrates described the disease as podagra, chieragra, or gonagra, depending on whether the big toe, wrist, or knee joint was involved. However, Sydenham's description in the seventeenth century is still one of the best clinical pictures of the disease.

For clarity in discussing the natural clinical course of the disease, Gutman's[1] arbitrary division into four phases seems to be the wisest, namely (1) asymptomatic "essential" hyperuricemia; (2) acute gouty arthritis; (3) intercritical gout; and (4) chronic tophaceous gout.

"Essential" hyperuricemia, the common denominator of all four phases, is probably more prevalent than is generally realized but usually is of such minor degree that no clinical manifestations of the disease may appear in the lifetime of the individual. To support this contention, several observers have determined serum urate levels in the families of patients with manifest gout. Talbott[2] found that 25 per cent of 136 asymptomatic blood relatives of twenty-seven gouty patients had serum urate levels exceeding 6 mg. per 100 cc. Thus, it appeared that "essential" hyperuricemia occurred frequently in these families as an inborn error of metabolism, though only a minority of these developed

1. Gutman, A. B. and Yu, T. F., in Dock, W., and Snapper, I., Advances in Internal Medicine, Vol. V, p. 227-302, Year Book Publishers, Inc., 1952.

2. Talbott, J. H.: Serum urate in relatives of gouty patients. *J. Clin. Invest.* 19:645, 1940

the clinical symptoms of gout. This is predominantly true among women, for while there were a considerable number of women in the "essential" hyperuricemia group, women compose only about 5 per cent of patients with manifest gout and they are usually in the postmenopausal age. The significance of this sex difference, as well as the fact that normal serum urate levels in women is lower than in men, is still unexplained. In this discussion of hyperuricemia other causes must be excluded, notably polycythemia, leukemia, multiple myeloma, or kidney disease. Furthermore, in some cases definite hyperuricemia may be intermittent so that its presence may be missed, or urinary clearance of urate may be sufficient to compensate for over production of serum urates.

CLASSIFICATION

Acute gouty arthritis—This term refers to the classic, full-blown attack, which usually comes on suddenly over a few hours' time, frequently in the early hours of morning. What begins as a few premonitory twinges of pain or stiffness becomes an extremely swollen, red, hot, and exquisitely tender joint in a few hours. Inspection of the area reveals all the signs of inflammation resembling an extensive cellulitis. Any garments, or even bed clothes, over the affected member are most uncomfortable, and in some instances the onset is so abrupt that, when occurring in the foot, the shoe must be cut to remove it. Some individuals may suffer with anorexia, nausea, and mild depression. A low-grade fever is not unusual and may be associated with leukocytosis and elevated sedimentation rate.

The acute attack lasts from a few days to several weeks and gradually subsides with complete freedom of symptoms and a normal joint until the next attack, which may be months or years later. Characteristically, the first attack occurs in a male over the age of thirty years. However, 5 per cent of the cases occur in women, although on the whole in a slightly older age group. Subsequent attacks may occur as often as every few months or as infrequently as years apart, but usually the pattern is one of gradually more frequent and more prolonged attacks. As the acute attack subsides, redness and tenderness diminish, pitting edema may be elicited, and the skin overlying the joint may itch and desquamate. This latter occurrence is uncommon in other forms of joint disease and is an important point in differential diagnosis.

Podagra—Podagra, or gouty arthritis in the metatarsophalangeal joint of the big toe, is commonly thought of as a synonym for gout. Although it is true that this joint is involved in the first attack in more than half the cases and in more than 90 per cent of the cases ultimately, *any* joint may be involved in first or subsequent attacks. In general, joints of the lower extremities are more frequently involved than those of the upper, and the peripheral joints more frequently than the proximal. The first attack is usually monarticular and indeed this may persist for many years, but progression from one joint to another with variable asymptomatic periods between occurrences is a characteristic course. Ultimately, multiple joint involvement may be noted, one region being involved as another improves.

Certain factors play a very definite role in the precipitation of an acute attack. It is more than coincidence that many patients can attribute an

TOXIN SPONGE . . .

BY THE SPOONFUL!

Resion®

POLYPHASIC ADSORBENT DETOXICANT SUSPENSION

RESION . . . a delicious suspension of *polyphasic*[1] adsorbents . . . is "the treatment of choice for diarrheas of the type the physician is called upon to treat in his everyday practice."[2]

FOR DIARRHEA AT ANY AGE, whether due to food poisoning or to bacterial or viral infections, RESION gives prompt relief.

RESION has controlled even the most stubborn nausea and vomiting of pregnancy, and is effective also in the management of food poisoning, flatulence, griping and symptoms of gastroenteritis and ulcerative colitis.

RESION is a suspension of polyamine methylene resin, sodium aluminum silicate and magnesium aluminum silicate.

SPECIFICALLY DESIGNED to adsorb and remove toxins and irritants from the intestinal tract, RESION is "totally insoluble and non-toxic."[1]

RESION is supplied in wide-mouthed bottles of 4 and 12 fluidounces.

1. Exper. Med. & Surg. 9:90, *1951. 2. Rev. Gastroenterol.*, 19:660, *1952.*

THE NATIONAL DRUG COMPANY *Philadelphia 44, Pa.*

Resion . . . *for more rapid, more complete control of*

DIARRHEA . . . INFANTS AND ADULTS

NAUSEA OF PREGNANCY

FOOD POISONING

ENTERIC INFECTIONS

acute attack to overindulgence in diet, liquor, or exercise. A long automobile ride, hunting or fishing trip, slight trauma, or infection may precede an acute attack. Certain therapeutic procedures, such as injection of liver extract, salyrgan, insulin, ergotamine tartrate, thiamine chloride, and other agents, may be followed by an acute gouty manifestation, and of course the possibility of gout in the postoperative patient with acute joint symptoms is well known.

As one would surmise from these facts, the onset of chronic tophaceous gout is insidious. As the urate forms in the body faster than it can be disposed of, it appears to have a predilection for cartilage, synovial membranes, bursae, ligaments, tendons, skin, and kidneys. Deposits that are sufficiently close to the surface to be seen appear as tophi. One of the favorite locations is the cartilage of the ear where, when small, only careful inspection may bring them to light. Indeed, such small tophi are frequently the only external manifestations of chronic gout. The precipitated urate crystals act as foreign bodies with typical inflammatory reactions and when occurring about articular structures cause pressure changes and degeneration. Persons thus afflicted may present swollen, mildly painful joints which are grossly deformed but differ from rheumatoid arthritis in that instead of the diffuse deformity there is a nodular, discrete, firm mass or masses. Weight bearing may be most uncomfortable, function markedly impaired, and in extreme cases the skin may ulcerate with extrusion of the chalky white contents externally. The high incidence of renal disease is a common and important association of chronic gout, and is a common cause of death. At necropsy an appreciable amount of urate deposits may be found, chiefly in the collecting tubules, as well as nephrosclerosis and pyelonephritis. A high incidence of generalized arteriosclerosis and renal calculi is also frequently associated with this disease.

ETIOLOGY

Is hyperuricemia due to (1) an excessive rate of production of uric acid, (2) a decreased destruction of uric acid, or (3) an impaired renal excretion of uric acid? Whereas it has been assumed for many years that uric acid was predominately formed by the body as a result of the breakdown of exogenous purines, in recent years, with the use of isotope technics, it has been shown that in additiion to the origin from ingested nucleoproteins and nucleotides, uric acid may be formed as a result of breakdown of endogenous nucleic acid synthesized in the body as well as by direct biosynthesis from simple carbon and nitrogen compounds. This work has been recently well summarized by Gutman.[1] Decreased destruction of uric acid does not seem a plausible explanation, for our knowledge of uric acid metabolism in man does not seem to substantiate this as a significant factor even in the normal person. While there is much controversy in regard to the basic cause of hyperuricemia, it would seem that thus far facts support the theory of overproduction of uric acid. The fact that some patients with gout show an excessive urinary uric acid excretion substantiates this view[3] While impaired renal function with diminished renal excretion of uric acid is an important factor, it is usually a secondary one contributing to

3. Friedman, M., and Byers, S. O., *Am. J. Med.* 9:31, 1950.

the hyperuricemia, particularly in the later chronic phases of gout.

Intercritical gout—This term refers to those periods between the acute attacks when the individual is completely asymptomatic and has resumed his prior status of "essential" hyperuricemia. In some persons the intercritical periods between acute attacks may be years in duration over an entire lifetime, but in more severe cases there may be a gradual and progressive shortening of these periods. As time passes there is more residual stiffness, swelling, and tenderness in the joints until there is a gradual merging of the intercritical phase into the stage of chronic tophaceous gout.

Chronic tophoceous gout—This, the fourth phase of gout, is inherently clinically and etiologically different from acute gouty arthritis. There can be no question that the manifestations of chronic tophaceous gout are due to deposition of urate in the tissues.

In most mammals uric acid is converted by uricase to the more readily soluble allantoin. However, man appears to lack uricolytic enzymes so that uric acid must be disposed of as such. Excretion of the uric acid is chiefly through the kidney in the form of urate, although small quantities are also excreted in the gastric and intestinal juices, bile, saliva, and sweat. In the normal healthy person, these routes are sufficient, but in gout the body is frequently unable to excrete adequate amounts in this manner and, as a result, uric acid is deposited in the tissues. This fact is well demonstrated by newer developments using isotope technics with labeled uric acid. Several groups of workers have been able to estimate the miscible pool of uric acid and the rate of its turnover in the normal and gouty individual. The miscible pool refers to the amount of uric acid present in the body in a form capable of prompt mixing with intravenously injected N^{15} labeled uric acid. With these technics it has been shown that in normal man a pool of 1.2 Gm. of miscible uric acid is present in the body, and that from 50 to 75 per cent of this quantity is daily replaced by newly formed uric acid. In gouty subjects the miscible pool of uric acid is increased from 3 to 4 up to 30 times this amount in advanced cases of tophaceous gout. By this means it is possible to establish the presence of increased deposition of urate in the tissues before it is demonstrable clinically or roentgenographically.[1]

From these statements it is apparent that all dietary proteins, fats, and carbohydrates are potential precursors of uric acid and must be considered in any dietary management of the disease. Many have assumed in the past that acute gouty arthritis attacks also are due to elevated uric acid, but most observers today do not favor this view. *There is no correlation between serum urate levels and symptoms.* Thus, uric acid taken orally or intravenously, or injected into joints or tissues, will not cause an acute attack in either the gouty or normal person. Also, many individuals with hyperuricemia secondary to other causes, that is, renal disease, will never develop gout. Another supporting observation is that the acute gouty attacks seldom involve the joints with definite demonstrable urate deposits but tend to migrate and involve other joints. Another theory to explain the acute gouty arthritis attacks has been allergic in nature, but little supporting evidence in working with antihistaminics (Gut-

man), skin tests (Hench), or diets, has been forthcoming. Recently, the application of Selye's concepts to the known precipitating factors of acute attacks, along with the response of ACTH and cortisone, has presented an attractive source of contemplation in regard to the role the pituitary and adrenal glands may play in this phenomenon. Unfortunately this is only theory, and no real light has been shed on the etiology of the acute attacks in gout. It is possible that some precursor or degradation products of uric acid may be the cause, but this, too, has no direct supporting evidence.

DIAGNOSIS

The diagnosis of gout is dependent on the history of recurrent acute attacks of an essentially monarticular arthritis which is sudden in onset, transitory in character, and subsides spontaneously in a relatively short time with complete disappearance of clinical signs and symptoms. Early in the disease this may be the only basis for diagnosis, for hyperuricemia in this stage may be transitory as shown by the fact that figures may be found in the literature pointing out that from *10 to 30 per cent of gouty individuals may have a serum urate level within normal limits.*[4,5] It is hoped that these figures may be lowered as these patients are more carefully studied and our technics of determination improved. The appearance of tophi, too, may be erratic and though frequently present early in the disease, is more often confined to later years of the disease. McCracken *et al*[6] found that in 750 reported cases of gout, 45.7 per cent of the patients had visible subcutaneous tophi. Thus, one can easily see that a careful history and awareness on the part of the physician of the possibility of this diagnosis in joint disease is the prime factor in making the diagnosis early in the natural course of gouty arthritis.

It is a simple matter for the physician to confirm his clinical diagnosis of gout in those patients who present definite tophi. A small amount of chalky white contents can easily be removed and examined microscopically for the presence of the typical uric acid crystals. Thus, a presumptive diagnosis of gout becomes a definitely confirmed one.

TREATMENT

From the foregoing discussion one might well deduce that the treatment which is to be applied in any given situation depends to a great extent on the particular phase of the disease at the moment. Thus, the individual with "essential" hyperuricemia who has never had an acute attack of gouty arthritis probably needs no management other than a word of caution and perhaps prudent moderate diet restriction with alcoholic abstinence.

Colchicine—On the other hand, the patient with acute gouty arthritis is most fortunate in having one of the oldest drugs known available for his use. Colchicine, which has been used specifically for gout since the fifteenth century and has no other known therapeutic value in medicine, is still the drug of choice in the treatment of the acute attack. Its mode of action is unknown and there is no demonstrable effect on the serum uric acid level or urinary excretion which can be attributed to the drug. Treatment should be

4. Comroe, B. I.: Arthritis and allied conditions. P. 904. 3rd Edition. Philadelphia: Lea and Febiger, 1947.
5. Hench, P. S.: Gout and gouty arthritis: in Cecil, R. L. and Loeb, R. F. (ed.): *Textbook of Medicine by American Authors*, p. 605, 8th ed. Philadelphia, W. B. Saunders Co., 1951.
6. McCrackan, J. P., *et al.*, *J.A.M.A.* 131:367, 1946.

started at the earliest sign of an attack in order to bring about adequate results.

Colchicine is usually given in an initial tablet dose of 1 mg. followed by 0.5 mg. every 2 hours until either relief of symptoms or toxic symptoms of colchicine have occurred. The latter consists of nausea, vomiting, diarrhea, or a mixture thereof. The total dosage necessary to produce these symptoms varies widely but is very close to the therapeutic dose in each case. By keeping accurate count of the amount taken, the patient should be able to halt his total dosage in subsequent attacks just short of toxic symptoms, or at least minimal manifestations, and still maintain the beneficial effects of the drug. Relief of the severe acute pain usually follows in a matter of a few hours or less, although minor pain, swelling, and tenderness may persist for longer periods. Fortunately, other than the toxic manifestations mentioned, no serious complications of colchicine therapy need be feared.

ACTH and Cortisone—Since the advent of ACTH and cortisone, an addition has been made to the armamentarium for the treatment of acute gouty arthritis. ACTH gives a rapid and satisfactory response in the majority of cases and usually in those cases refractory to colchicine therapy. On the other hand, there are some cases which do not respond to ACTH in which colchicine will cause a remission of symptoms. Also, some cases will suffer an exacerbation of symptoms following discontinuance of ACTH therapy, the cause of which is not known any more than the mode of action.

It has been demonstrated that ACTH therapy will increase the uric acid urinary excretion and a lowering of the blood serum uric acid, but the degree of relief of symptoms is much greater and completely out of proportion to the amount of change which might be attributed to change in uric acid concentrations.[7] In the early phases of an acute gouty arthritis attack, an injection of 25 mg. of ACTH every 6 hours for two or three doses may be sufficient to abort an attack. In the more severe and well established attacks, initial dosages of 50 mg. may be necessary with gradual reduction of the total daily dose from 150 mg. to 20 or 25 mg. over five to seven days' time. By such *slow reduction* of dosage, most exacerbations secondary to abrupt termination of treatment can be prevented.

Many physicians use colchicine in combination with such an ACTH schedule as mentioned with good results, giving 1 to 2 mg. of colchicine daily and continuing the dosage for several weeks after ACTH is stopped.

Cortisone has also been used but has rather uniformly given more delayed and less consistent results. It has been reported that compound F (hydrocortisone) when injected into the affected joint or bursa gives very rapid relief.

Supportive treatment—In spite of the dramatic relief usually afforded by these forms of treatment, one should never forget the age-old measures of supportive treatment. A soft diet, forced liquids, bed rest, liberal use of salicylates and sedatives, and a trial of warm or cold compresses locally should all be carried out.

In both the intercritical and chronic tophaceous phases of gout

7. Thorn, G. W., *et al.*: Studies on relation of pituitary adrenal function to rheumatic disease. N. Eng. J. Med. 241:529, 1949.

the physician has two primary aims: (1) to prevent the recurrence of acute gouty arthritis and (2) to prevent the development of tophaceous deposits and the complications thereof. Since the mechanism of acute gouty arthritis attacks is not known, our approach to this problem is necessarily an oblique one. Naturally, those things which may precipitate an attack in the individual patient must be ferreted out by a careful history and the patient made aware of their significance. The Saturday night poker party with liberal beer consumption, the annual long motor trip, and lavish holiday feasting which is so common may all be related factors which may easily be controlled. Generally, it is agreed that consumption of all alcoholic beverages is taboo for the gouty patient.

Specific therapy — Specific therapy in an endeavor to prevent recurrent acute attacks is a controversial subject. Many physicians believe that a prophylactic dose (frequently 1 or 0.5 mg. every day or every other day) of colchicine definitely reduces the likelihood of recurrent attacks. Others do not favor this view. Cortisone or ACTH do not easily lend themselves to any long-range prophylactic program and because of their disadvantages have not been used extensively.

In order to prevent the possible formation of tophi and the chronic phase of gout one naturally attempts to lower the blood serum urate level and also indirectly hopes that the frequency of the acute attacks will be diminished. In order to do this, means must be devised to (1) limit uric acid formation and (2) increase renal excretion of urates.

Since, as has been previously discussed, uric acid is formed not only from exogenous purines but also by endogenous cellular biosynthesis, it would appear that we have little objective scientific data on which to base a severe or moderate dietary restriction. However, most observers feel that there is definite clinical improvement in those patients placed on a low purine, low fat diet with additional restriction of meat, fish, and fowl. To support this, reports may be found of marked decrease in acute attacks in gouty individuals experiencing food shortages in war-torn Europe. Also one is reluctant to unnecessarily increase uric acid precursors in the diet above actual dietary needs.

In conjunction with dietary restriction, many uricosuric agents have been used with variable results. Cinchophen has been used for many years in this regard with good results. However, its severe toxic properties, although infrequent, have led most physicians to turn to other agents.

Salicylates in proper dosage are definitely uricosuric. Their effect is obtained by inhibition of tubular reabsorption of urate. In dosages of 3 gm. per day of aspirin or sodium salicylate the effect is minimal. *With smaller doses there may be an actual renal retention of urate with elevation of blood serum levels.* The optimum dosage, therefore, is from 4 to 5 gm. per day. Simultaneously the urine should be kept alkaline by the use of sodium bicarbonate. Administration of from 2 to 4 gm. three times per day should suffice, and the urine alkalinity can be easily checked with litmus paper by the patient himself. By this means the precipitation of urate stones in acid urine can be prevented.

Ideally, salicylates are given in constant daily dosage indefinitely. However, it has been reported that after a few months, the individual

develops a tolerance to the drug with the reappearance of hyperuricemia to pretreatment levels. Others have been able to maintain an uninterrupted dosage for six to nine months with actual mobilization and excretion or urate from tophi as evidenced by diminution in size of visible tophi.[8] Because of the severe symptoms of tinnitus, gastrointestinal upsets, and hyperventilation caused in some individuals on such high salicylate dosage, most workers have used intermittent schedules. In these, 4 to 5 gm. of salicylate is taken 3 or 4 days a week (along with sodium bicarbonate), followed by 3 or 4 days' rest. The objection to this program is the fact that while urate excretion is enhanced during the treatment period, there is actually some retention of urate after cessation of salicylate so that the net over-all result is not far different than that of a hyperuricemia without uricosuric treatment.

From these facts one can easily see there is considerable confusion as to the best program to follow and perhaps each individual patient is best studied separately and a program worked out to fit his needs. It would seem best to first place the gouty patient on a prolonged uninterrupted high dosage salicylate program combined with diet restriction. If this is well tolerated, and the hyperuricemia is well controlled both symptomatically and chemically, no definite time limit should be set. If it is not well tolerated and salicylism appears, then the intermittent dosage program may be adopted by necessity.

Recently carinamide and benemid have been utilized as uricosuric agents. These substances were originally used in enhancing blood levels of penicillin and PAS, but in working with them it was noted urinary uric acid excretion was increased. This mechanism is primarily by inhibition of tubular reabsorption. The side reactions, though mild, with carinamide were sufficient to cause it to be discarded in the treatment of gout. However, Gutman has done considerable work with benemid in the last two years and found it a highly successful uricosuric agent.[1,8] In uninterrupted daily doses of 0.5 to 1 gm. per day, closely checked by uric acid blood levels and urine urate excretion, he has found it possible to maintain a satisfactory uricosuric response and sustained fall in serum urate levels over a prolonged period of time. On such a schedule reduction in size and even disappearance of tophi have been witnessed.[8] Side reactions to the drug have been minimal and so far not serious. However, insufficient time has elapsed to establish the exact status of this drug and indiscriminate use is certainly not advisable.

PROGNOSIS

It should be pointed out that prognosis in gout is poorest among those whose symptoms appear early in life and best in those whose symptoms come late in life. Gout, like diabetes mellitus, must be regarded as an incurable disease of metabolism, but one in which treatment must be continued for life in order to postpone or prevent recurrences. It is hoped that faithful adherence to treatment will modify the course of the disease by reducing the severity and frequency of acute attacks and ultimately reduce or retard the occurrence of chronic tophaceous gout.

8. Yu, T. F., and Gutman, A. B., *Am. J. Med.* 11:765, 1951.

Juvenile Hypertension

Juveniles are found to be hypertensive much more frequently than previously observed.

A. KAPPERT, M.D., *Berne, Switzerland*

Within the last few years a considerable increase of hypertensive patients has been observed. American statistics show 40-50% of the population over 40 years of age suffer from hypertension. Juveniles, too, are found to be hypertensive much more frequently than could be detected in the past. The sequelae of hypertension has increased, so that in the United States 15% of all deaths are due to sequelae of hypertension.

In the etiology of juvenile hypertension a complex disturbance of the regulation of the entire circulation has to be considered. Neuro-hormonal factors play the decisive role while renal pressor substances are of lesser importance. Pathogenetically, the adreno-sympathetic system and the piloting diencephalic centers are of particular interest.

It is difficult to establish 'normal' blood pressure values in juveniles. In American statistics, the borderline values in the age group 20-40 have been determined as being 149/90 mm.Hg. According to Master and associates, about 29% of all males between ages 20-29 would be hypertensive if the above given values would be taken as the basis for the diagnosis.

The clinical classification of juvenile hypertension is involved. It is well known that only in about 10% of hypertensive cases, diseases of special organs can be found as cause of blood pressure elevation. Acute and chronic nephritis, hydronephrosis, stenosis of ureter, cystic kidney, pheochromocytoma, cancer of the adrenal glands, Cushing's syndrome, acromegaly, hyperthyroidism, cancer of the thymus gland; isthmus

* This paper first appeared in German in a Swiss Medical Journal *Periodical Communications to the Swiss Physicians*, December 1952.

stenosis of the aorta, arteriovenous fistulae, heart insufficiency (Sahli), heart block; encephalitis, chronic carbon oxide intoxication, poliomyelitis, tumors, trauma—in all these cases the term secondary or symptomatic hypertension is applied.

The greater part of primary juvenile hypertensive cases, not caused by impairment of special organs, are the types which have been known as vasomotor lability, vegetative or neuro-circulatory dystonia, etc. The circulatory dynamics in these cases is influenced by over-irritable diencephalic centers which are exposed to exogenic and endogenic stress. The lability of the circulatory regulation is so marked that average daily strain prompts either paroxysmal or permanent hypertension. Essentially, the systolic values are elevated with simultaneous increase of the pulse pressure, while the diastolic pressure does not rise equally. The eye fundus and the EKG do not reflect signs of diffuse or localized involvement of the circulatory system.

The second group includes the primary hypertensive cases proper. This is but an early form of essential hypertension. Essential hypertension is characterized by disturbances in the realm of the arterioles exhibiting vasoconstrictive processes in certain organs, which slowly bring about organic alterations. Subjectively one may find in the early stages of essential hypertension, pain in the back of the head in the morning, disturbances of sleep and vision, dizziness, fatigue, etc. Important are the objective signs which may be established early in the course of the disease of "cardio-vascular hypertrophy" which can be proved in the ocular fundus, the EKG, chest roentgenogram and with kidney function tests. From these initial disorders the juvenile hypertension develops, with changing rapidity, into the typical syndrome of essential hypertension. The end stage is characterized by the break-down of certain circulatory regions in the forms of apoplexy, myocardial infarction, cardiac insufficiency or uremia.

A third form is the so-called malignant hypertension (malignant nephrosclerosis) which can be seen predominantly at the ages between 20 and 45. Juvenile hypertension may occasionally transform into this malignant and fatal type. The prognosis is poor. Clinically, diastolic hypertension of over 130 mm.Hg, grave alterations of the eye fundus with hemorrhages and exudates in the retina, pathological left axis deviation of the EKG and abnormalities of the kidney function, are the prevalent findings. Uremia, heart insufficiency, and, more rarely, apoplexy, determine the terminal phase. The cause of the malignant form of the juvenile hypertension is not known.

The juvenile hypertension—second group—in which e a r l y organic changes can be detected, has hardly a better prognosis than that of malignant hypertension. The condition may remain stationary for years; but, generally, the course is progressive and endangered by the involvement of special organs. The neurocirculatory dystonia, on the other hand, may be assessed differently depending mainly on whether the hypertension remains transient or becomes permanent. In these latter cases the possibility of a "prehypertension" must be borne in mind.

In cases of juvenile hypertension without organic findings, several factors may be helpful in predicting the development of the case. The most important factor is heredity. When both parents are hypertensive, 47% of the offspring may also become hy-

pertensive, while only 3% of children may later suffer from hypertension when both parents were normotensive. Obesity also is a significant element. Although the influence of overweight is particularly distinct after age 40, the combination of overweight and hypertension has also been frequently observed in children.

As recent investigations have evidenced, daily worries and strain are a great stress for the circulatory system and may cause, in patients with neuro-circulatory dystonia, intensive hemodynamic changes. Because of inadequate reactions, conflict situations may prompt hypertension. Such patients show, when discussing the actual difficulties of their life situation or past conflicts, sudden constriction of the kidney arterioles with rise of the renal vascular resistance by 40 to 50%. In this connection Selye's alarm reaction and adaptation syndrome should be mentioned. Stress causes increased secretion of adrenal hormones. The hyperfunction of the adrenal cortex occasions the secretion of gluco-corticoids and mineral-corticoids which leads, in the liver, to the formation of hypertensinogen and, in the kidneys, to the production of renin, so that angiotonin, with its hypertensive effect, is formed. In the last years the hormone of the adrenal medulla: nor-adrenalin has achieved a special role in the problem of hypertension. By stimulation of the sympatheticus it is secreted together with adrenalin and causes hemodynamic alterations in man, such as increase of the peripheral vascular resistance and of the diastolic blood pressure, like those seen in essential hypertension. The shunt-mechanism as demonstrated by Trueta also can be prompted by nervous, sympathetic stimuli. It causes disturbances in renal circulation with hypoxemia of the renal cortex and, herewith, elevation of blood pressure. It is understandable that frequent repetition of nervous stimuli in the daily 'stress and strain' in patients with neuro-circulatory dystonia may finally end up in permanent hypertension with all its possible sequelae.

It can be concluded that individuals with emotionally determined transient hypertension are disposed to develop essential hypertension if they are exposed to conflicts and overwork and when they have little opportunity for relaxation and rest.

The increase of juvenile hypertension is a consequence of modern conditions. A preventive measure is change in the way of living, particularly avoidance of emotional pressure, reasonable limitation of sports, regular relaxation, adequate nutrition, sufficient sleep and self-restriction in the use of alcoholic beverages, coffee, and nicotine. In predisposed persons particular attention should be given to the choice of occupation.

Prophylaxis is more important than treatment. With early diagnosis of secondary hypertension and of the juvenile form of essential hypertension as well as with thorough analysis and appropriate management of juvenile neuro-vegetative hypertension the prognosis of all types of juvenile hypertension can be much improved.

Some Notes on Dysmenorrhea

Hormonal treatment and psychotherapy are the treatments of choice in functional dysmenorrhea.

W. E. LOCKHARDT, M.D., *The Lockhardt Clinic, Alpine, Texas*

Functional dysmenorrhea is a manifestation of frustration of the natural reproductive drive. It occurs in gifted, ambitious women. It is accentuated by the economic and social circumstances of our day which require years of cultural endeavor and delayed reproduction. Have a baby alone is not the complete answer, for many women have a recurrence of functional dysmenorrhea. A complete sex life including an effectionate and loved mate, a natural sex life without fear or guilt and social and economic adjustment is the answer. Functional dysmenorrhea is a reaction of disgust, probably with reverse peristalsis of the uterine musculature as a physical mechanism. It represents an effort on the part of the woman's primitive nature to derail by pain, depression, anxiety and inconvenience the high vaulted ambitions of the moral and cultural facets of the woman's personality. Dilatation of the cervix possibly because of the subconscious suggestion of sex and the reproductive function including hospitalization, helps in some cases. Artificial pseudo-pregnancy with cessation of ovulation and menstruation brought about by the administration of large doses of estrogen, such as 100 mgm daily of Desplex as recommended by Karl Karnaky, M.D., continued for several months is more effective. But the best treatment is personal guidance, helping the woman achieve a well balanced life in these strenuous times.

Dysmenorrhea that is the result of endometriosis deserves special attention because it can be diagnosed in most cases without surgery and can be effectively treated without surgical or X-Ray castration. This is especially important in women be-

fore the menopause, when endometriosis is a most urgent problem. Surgeons are resisting the idea — quite as many thyroid surgeons resisted the thiouracil drugs — but it is now a crime against humanity to castrate a young woman because of endometriosis. Artificial pseudo-pregnancy with cessation of ovulation and menstruation for several months causes a miraculous dissolution of endometriosis, with a return of normal menstrual and reproductive function after treatment is discontinued. The drug of choice is Despler as mentioned above. If necessary the treatment can be repeated.

Detection of Cardiac Enlargement

It is claimed that the method here briefly detailed "gives results that correspond closely with skilled percussion and fluoroscopy and are based upon changes of sound sharper and more definite to the ordinary ear than those of unskilled (usually too heavy) percussion."

The essential features of the method are as follows. With the patient breathing quietly and standing or sitting in the erect posture, the examiner places his stethoscope over the fifth left cartilage near the sternum and listens to the first heart sound, moving the stethoscope horizontally outwards, 1 cm. at a time, towards the left axilla. "Sooner or later, a sudden, quite marked lessening in the loudness of both sounds will be noted." This point, which should be marked with a skin pencil, "will correspond closely to the left border of dullness in mid-respiration as determined by expert percussion."

The same procedure is followed in the fifth space and under the sixth rib to determine whether there is any enlargement to the left at the apex, or any downward displacement. The position of the right border of the heart is elicited in the same manner, and of the upper border at the junction of the third left cartilage and the sternum.

The method is described in the hope that the busy practitioner who is not too sure of his percussion may find it a help, either by obtaining reassurance when he has feared abnormality, or, more important, by being enabled to detect an abnormality that he might otherwise have missed.

(F. W. Palfrey, *New Eng. J. Med.*, 247:612, 1952)

CASE REPORT

Multiple Carcinomas

Case of a thirty-seven year old female patient, married, with one child. Patient was first seen in October, 1936 for a check up by her family physician. Her father had died at age forty-eight from pneumonia, the mother at age sixty-three from nephritis, two brothers had died in infancy, three sisters were living and healthy. Patient herself had been operated on twelve years ago, in 1924, and an oophorectomy had been performed. For a short time she had suffered from malaria. After taking quinine the attacks subsided and she did not experience any recurrences. The physical examination in 1936 was essentially negative.

The patient was admitted to the Clinic in August, 1948. In a letter the family physician stated that he had seen the patient because of an ulcerated mass on the cervix.

As to the family history, the patient stated that all three of her sisters, now 52, 50, and 46 years of age respectively, have goiters. Regards the personal history she stated that she had been "nervous" since 1938. It started with "shaking" at night, rapid heart beats and absentmindedness. Since 1933 she had noticed a goiter which was swelling occasionally and then made breathing and swallowing difficult. She had been taking Lugol solution intermittently. For the last month she had stopped taking Lugol solution. Hypertension was first noticed in 1946. The highest systolic reading was 180. The menstruation had started at age seventeen, was regular at four weeks intervals, with a duration of seven days. It has been irregular for the past five months and she had experienced hot flushes and increased nervousness. Since 1945 she had observed vaginal discharge. She complains now of pains in her left lower chest on overexertion or stooping. Since 1938 she had headaches associated with pain in the goiter about fifty times a year, and nausea about twelve times a year. At night she awakens with dyspnea associated with distress in the left side of the chest, radiating pain to the left arm, neck, and shoulder plate. Because of the menopausal symptoms she received shots after which she began to flow again bright red blood, in May, 1948, and since then continued spotting at intervals of three to four days.

The physical examination showed a 5′5″ tall, rather lean female; weight one hundred three pounds. The pulse was 110 per minute, the blood pressure 145/90, the temperature 99F, gait and posture normal; the skin was moist and warm; eyes and ears were normal; the neck showed a symmetrical diffuse swelling at the base. One inch anterior to the lobe of the left ear there is an irregular defect consisting of smooth skin without hair and a dry crust, measuring about 7 times 7 mm. The teeth are in good repair. Chest expands equally, there is no evidence of cough, or dyspnea. There is some cyanosis of the nail beds; heart action is regular, 96 per minute. The breasts are atrophic, no nodes are felt and the axillae are negative. The abdomen presents abnormal tension but no other abnormality except a scar in the left lower quadrant. The pelvic examination shows that the cervix is replaced by ragged bleeding tissue which is soft and tears readily. The cervical canal cannot be identified; the cervix is mobile and the broad ligament is not involved. There are no adnexal masses or tenderness. The nervous system is negative. The laboratory tests show a B.M.R. of plus 22; urine is acid, contained neither albumin nor sugar; there are 6-8 WBC per hpf and occasional calcium oxalate crystals. The blood count reveals 4,760,000 RBC, 7,000 WBC, and 82% hemoglobin. The Kahn reaction is negative. The electrocardiogram is normal in all leads. The biopsy of the cervix shows that the specimen consists of several irregular, reddish-gray fragments of tissue. The microscopical examination reveals several segments of cervical tissue. There are numerous masses of epithelial cells that form glands which are fairly well delimited. However, in several areas the epithelial cells appear to be invading into the fibrous tissue and muscle tissue of the cervix. The cells themselves show only moderate variation in size, shape, and staining characteristics. However, because of the invasive qualities and the moderate variation, the diagnosis adenocarcinoma of the cervix, grade II, was made. The x-ray showed that the transverse colon is redundant and reaches the pubis. The descending colon appears atonic in all films. The diagnosis was colitis. The chest plate showed normal heart and lung. The following diagnoses were made: adenocarcinoma of the cervix, grade II, stage I; diffuse colloid goiter; and hypothyroidism; basal cell carcinoma of the left cheek, mild secondary anemia, and questionable angina pectoris. The staff decided not to operate for the present but to refer the patient to a radiologist for pre-operative treatment.

The report from the radiologist, received two weeks after discharge from the Clinic, stated that his findings confirmed the submitted report in every detail. Patient was hospitalized and radium and X-ray therapy administered.

The Clinic was informed that four years later, in July, 1952, the patient had died from carcinoma of the thyroid gland, at fifty-three years of age. A report from the attending physician stated as follows: After termination of the x-ray treatment in 1948, the patient remained well until 1950, then it was noted that the diffuse colloid goiter was enlarged and a thyroidectomy was performed. The pathologist's examination revealed that the tumor was a primary carcinoma of the thyroid gland. Deep x-ray treatment was administered to the chest and neck region. Repeated follow up studies of the patient showed no evidence of any recurrence or spread of the adenocarcinoma of the cervix. Evidence of recurrence of the

carcinoma of the thyroid gland, however, became apparent in the fall of 1945 by enlargement of the mediastinal nodes. X-ray treatment again was given to the chest but no improvement was observed. Within the first months of 1952, two large masses were noticed bilaterally in the kidney region. The consultant surgeon was of the opinion that these masses were metastases from the thyroid gland cancer. X-ray therapy was administered to the kidney regions. However, there was no response. Death occurred about one month after the last x-ray treatment.

Blood Protein Replenishment in Nephritic Edema

The chief cause of edema in the nephrotic stage of chronic glomerular nephritis is the reduction of osmotic pressure of the plasma resulting from a reduced albumin content. The latter is in turn attributable to urinary protein loss and insufficient protein synthesis. It follows that a high protein regimen is more effective than reduction in sodium intake or mere removal of fluid.

Although intravenous infusions of human plasma, concentrated human serum albumin, or protein hydrolysates have in general proved disappointing, the authors have found the blood-fibrin hydrolysate "Aminosol" (5 per cent) to be therapeutically effective. This preparation is salt-free and has an osmotic pressure which is twice that of plasma. Its daily injection in amount of 50 to 100 Gm. leads to an increase in the blood non-protein nitrogen level, which is, however, of little consequence, especially if the resting level is less than 75 mg. per 100 ml. Three cases illustrating the successful administration of this fibrin hydrolysate are cited.

Also described is an oral protein supplement ("Kralex"), which is a palatable preparation made from milk, with a high protein (60 per cent) and very low sodium (0.009 per cent) content, which the authors assisted in developing. It is readily tolerated in amounts which provide a protein intake of more than 150 Gm. per day.

(Marquardt, G. H. Cummins, G. M. and Fisher, C. I. *Quart. Bull. Northw. Univ. Med. Sch.*, 26:140-146, 1952.)

AIDS IN DIAGNOSIS

Pulmonary Cavitation With Negative Sputum

Pulmonary cavitation, especially in the upper lobes, is usually diagnosed by internists and general practitioners as tuberculosis, even though the sputum is not positive. It is true that this diagnosis is correct in many instances, but this is not because cavitation is specific for tuberculosis but because of all pulmonary diseases which may produce this condition, tuberculosis is the most common. It is also true that the sputum may be negative even though the patient has had cavernous tuberculosis for many years. However, before a diagnosis of tuberculosis is made in instances in which the sputum is negative and the roentgenogram reveals evidence of tuberculous symptoms, a thorough search should be made for other possible causes. This search should include Papanicolaou smears for malignant cells, fungus studies of the sputum, skin testing, and serologic tests for cavity-producing fungus diseases, cardiac evaluation, and studies of other organ systems for indications of polyarteritis.

These studies will aid in avoiding many erroneous diagnoses of tuberculosis and tragic delays in surgery, even though the final diagnosis must often be made by the pathologist.

(Balchum, E. G., and Zimmerman, J., *Dis. Chest* 22:68, 1952.)

Climacteric Following Supravaginal Hysterectomy

A study of 118 women who had had supravaginal hysterectomies with preservation of at least one ovary, before the age of forty years, and were less than forty-six years at the time this study was concluded.

Hot flushes appeared before the age of forty-one years in 36 per cent, the onset varying from one month to seven years after operation. In two-thirds of these women, the flushes occurred during the first two years. Menstrual disturbances were seen during the follow-up period in 29 per cent of these women, seven or eight of whom had hot flushes. Sixty-one per cent of the women were hyper-irritable, 29 per cent had a weakened memory, 92 per cent had gained weight, which gain exceeded 10 kilograms in 19 per cent of this number. Libido was unchanged in 66 per cent of the women, increased in 12 per cent, and decreased in 2 per cent.

Quantitative gonadotropin titers were ascertained in twenty-five women, and were found to be increased only in four (more than 3 mouse units). The postoperative incidence of climacteric was approximately 59 per cent. Ovarian dysfunction may well be attributable to an impaired ovarian blood supply produced incidentally to the operation.

(Knutsen, K., *Obstet. et Gynecol. Scand.* 31:1 1951.)

Pancreatic Insufficiency

Pancreatic insufficiency, with or without disturbance of the carbohydrate metabolism may be related to any of the diseases of the pancreas which cause destruction of impairment of function of the acinous glandular tissue, such as chronic pancreatitis, tumor, hemorrhage, or stones. The symptoms of pancreatic insufficiency are identical with those of indigestion and malnutrition due to lack of digestive enzymes. Minor degrees of the syndrome may remain unrecognized in chronic Alcoholism, Laennec's cirrhosis of the liver and disease of the gallbladder. Acute pancreatic insufficiency is caused by obstruction of the pancreatic duct by whichever pathology (stone, tumor, edema, etc.)—pain is the overshadowing complaint. Chronic pancreatic insufficiency reveals itself either by digestive (fullness, vomiting, diarrhea) or nutritional—metabolic signs and symptoms (weight loss, liver impairment, hypoproteiemia, hypocalcemia, vitamin deficiency, osteoporosis). In cases of severe and extensive pancreatic disease, diabetes mellitus may complicate the picture. In chronic pancreatic insufficiency, pain is not a factor. In children with chronic pancreatic insufficiency (mostly fibrocystic disease of the pancreas) bronchitis, bronchiectasis, or suppurative lung disease are frequent complications. The following laboratory tests are helpful: (1) microscopic and chemical examination of stools (fat, meat fibers—chemically, increase in neutral fat and nitrogen); (2) examination of duodenal juice obtained by intubation (decrease or concentration of enzymes, and, in chronic cases, decrease of volume and bicarbonate content); (3) Determination of response of lipase and amylase in blood serum to stimulation with secretin, Urecholine, neostigmin, etc. (in obstruction: increase of 50% or more in amylase, or lipase; in extensive acinous atrophy, however, such increase will not occur).

(C. L. Brown. *California. Med.* 77:172, 1952.)

Gastrointestinal Changes in Pneumoperitoneum

Pneumoperitoneum has assumed an important place in the non-surgical treatment of tuberculosis. The object of this study was to correlate the anatomical findings as observed in the gastrointestinal tract by means of radiologic examination, with the symptoms and disturbances arising from pneumoperitoneum.

The gastrointestinal studies were performed in a group of 37 patients immediately before initiation of therapy and again after six weeks and six to eight months following the collapse treatment. The typical anatomic changes which occurred with pneumoperitoneum included elongation and narrowing of the cardiac portion of the stomach, widening or dilatation of the fundus, anterior displacement and drop of the stomach. Weight loss was experienced by the majority of the patients with pneumoperitoneum. The other gastrointestinal symptoms were usually found to be of milder form. Little correlation was observed between the symptoms associated with pneumoperitoneum and the degree of anatomic changes.

(E. D. Bobrowitz, F. Slias and J. Ochs, *Am. Rev. Tuberc.*, 66:750, 1952.)

Identification of Types of Pulmonary Cancer In Cytologic Smears

The significant feature of the cytologic technique here proposed is —so it is claimed—that, with it, not only can the presence of cancer be detected in a very large percentage of the cases in which it is harbored, but its type may be recognized in 80 per cent of these. Thus a basis is afforded for prognosis as well as diagnosis.

The series of smears reported cover 341 selected cases of pulmonary cancer. The cases included were only those in which laboratory diagnosis gave conclusive evidence of malignant neoplasm, as confirmed by biopsies, either at the time or post-mortem. They were selected from a series of smears of sputum and bronchial aspirates submitted to the laboratory during the past 7 years by several hospitals and physicians.

The series of smears represented 183 ipidermoid carcinomas (8 of esophageal origin), 65 pleomorphic carcinomas, 43 adenocarcinomas (6 secondary to tumors elsewhere in the body), 41 anaplastic carcinomas (oat cell), 5 alveolar or terminal bronchiolar carcinomas, 2 bronchial adenomas, and one example each of malignant teratoma and fibrosarcoma.

The percentages of accuracy of diagnosis for the various types were: epidermoid carcinoma, 89.9%; pleomorphic carcinoma, 69.2%; adenocarcinoma, 81.4% for all types, and 78.4% for primary growth; anaplastic carcinoma, 83.5%.

Sputum smears have thus proved to supply better evidence for the recognition of the various types of malignant growth than do those of bronchial aspirates, it is concluded.

(N. C. Foot, *Am. J. Path.*, 28:963, 1952)

Fertility in Women

In each month in which ovulation occurs, there is a critical period from 6 (B. B. Rubengtein et al., *Fertil. & Steril.*, 2:1, 1951) to 12 (J. Rock, *New Engl. J. Med.*, 240:804, 1949) hours, during which the ovum may be fertilized. It would appear that the optimal fertility time would begin 48 hours preceding ovulation and last until 12 hours after escape of the egg from the fillicle. It has been agreed that the best method to determine the time of ovulation is by recording the basal body temperature. If a normal woman takes her early morning rectal temperature before arising, she will notice an abrupt fall in basal temperature near the middle of the cycle; this is followed by a rise higher than the temperature during the first part of the cycle. This high level is sustained until just before the next period so that the temperature curve for the entire cycle looks somewhat like the familiar square root sign. It is believed that secretion of progesterone by the corpus luteum is responsible for the higher temperatures in the second half of the cycle and, therefore, it has been assumed that ovulation occurs at the time of the temperature-fall. This theory, however, has its limitations. According to M. E. Davis and N. W. Fugo (*J. Clin. Endocrin.*, 8:550, 1948) 24 of 100 women who conceived had coitus after the low point had been passed and the temperature was rising.

(J. B. Doyle. *Ciba Clin. Symp.*, 1:23, 1952.)

THERAPEUTIC TRENDS

Erythromycin (Ilocytin)

"Preliminary studies of the new antibiotic, erythromycin, indicate that it affects mainly the gram-positive bacteria, its spectrum of activity being similar in many respects to that of penicillin. In addition, it is quite active against Hemophilus pertussis . . . It appears from these studies that after oral administration of erythromycin the substance is fairly readily absorbed from the intestinal tract and diffuses rather generally throughout most of the tissues. Erythromycin administered orally has a definite effect upon the bacterial floral of the intestinal tract. This effect is predominantly on Clostridium. Based on the studies herein reported, we administer erythromycin by the oral route every six hours. For the average adult the recommended dose is 0.4 to 0.5 gm. every six hours. Doses in excess of these amounts are frequently associated with evidence of gastrointestinal irritation, which may be manifested by nausea, vomiting and, on occasion, diarrhea. If gastrointestinal irritation occurs with the recommended dose, the dose may be decreased to 0.3 gm. however, this is the lowest dose that will regularly give adequate serum levels."

(F. R. Heilman, *Proc. Staff Meet., Mayo Clinic*, 15:285, 1952.)

Tuberculosis

Isonicotinic acid hydrazide is obtained as colorless crystals which are soluble in water. The crystals are bacteriostatic to M. Tuberculosis in a dilution of 1:60,000,000. It can be administered orally or subcutaneously. Ninety-two patients were treated representing all types of tuberculosis. The age ranged from 10 to 70 years. The temperature diminished, cough and expectoration decreased and the general condition improved. 10 patients received from 2 to 4 mg. per Kg. body weight per day orally. The dose for the remainder of the patients was up to 10 mg. per Kg. body weight. Doses of 10 mg. per Kg. had the fastest result but author recommends a dose of 5 mg. per Kg. body weight. The signs of toxemia due to tuberculosis such as fatigue, dyspnea, weakness subsided within a few days. The weight of most patients increased. The number of M. Tuberculosis in the sputum diminished in 25 instances and the sputum became entirely negative and 23 cases. X-ray examination showed improvement in 45 cases whereas 47 cases remained unchanged. Side effects are: constipation, difficulty in urination and fall in hemoglobin.

(E. Sivrieri. *La Presse Medicale*, 60:534, 1952)

Treatment of Sprue with Folinic Acid

All of the nine patients covered by this report had macrocytic anemia with an erythrocyte count of less than 2,500,000 per cubic millimeter of blood, in addition to megaloblastic bone marrow, glossitis, loss of weight, diarrhea and general weakness.

Folinic acid was given intramuscularly to three patients in doses of 100 to 400 units for twelve days (1 unit is stated to equal approximately 1 mg. of pure citrovorum factor). The response of the patients to this therapy was unsatisfactory hematologically and clinically. On the other hand, a rapid and satisfactory response was obtained in six other patients who received 1000 units of folinic acid for the same number of days as the first group.

It is concluded that folinic acid is qualitatively as effective as folic acid in the treatment of sprue, and that, furthermore, folinic acid is from ten to fifteen times as effective in the treatment of this disease than is folic acid.

(Romero, C. A., Vizcarrondo, R., and Rodrigrez-Molina, R., *Am. J. Med. Sci.*, 224:9, 1952.)

Epilepsy

Preliminary report on use of Hibicon (Lederle) as an anticonvulsant. Of 31 cases treated for a period of 2 to 20 months, both idiopathic and organic epilepsy, most of which had been treated with poor effect previously, 50% were greatly improved, 25% slightly improved, 25% not improved. Hibicon is N-benzyl-B-chloropropionamide. The clinical dosage was 500 mg., 4 to 6 times daily. No side effects or signs of toxicity were noted.

(L. A. Kaplan, St. Maslanka. *Dis. Nerv. System*, 13:88, 1952.)

Isoniazid With and Without Streptomycin

The response to the new drug used singly and in combination with streptomycin, was studied in two groups of patients with pulmonary tuberculosis.

Group I consisted of twelve patients (three women and nine men,) aged twenty-five to forty-nine years, who received 250 mg. of isoniazid daily by the oral route. Group II comprized eleven patients two women and seven men,) aged twenty-one to fifty-eight years, who received the same oral dose of isoniazid, but supplemented by a dose of 1 gm. streptomycin sulfate given intramuscularly on six days of each week.

A beneficial effect was experienced by a few of the patients only who received the isoniazid alone. This initial effect soon began to fade, however, and deterioration set in again. The latter state was accompanied by the excretion of resistant strains of tubercle bacilli in the sputum.

The second group of patiens fared quite otherwise. Here, the initial improvement was maintained for some 18 weeks up to the time this report was written. In other words, there has been a continued rapid amelioration in the sputum counts, in body weight, in the erythrocyte sedimentation rate, and in the clinical condition.

The combination of isoniazid with streptomycin is thus seemingly highly effective for the treatment of pulmonary tuberculosis, and thus is deserving of much more extended trials.

(Joiner, C. L., Machean, K. S., and Pritchard, E. K., *Lancet*, 2:843, 1952)

Barbiturate Poisoning

The overdoses of the so-called short-acting barbiturates such as secobarbital (Seconal), pentobarbital (Nembutal), vinbarbital (Delvinal) and amobarbital (Amytal) rapidly depress the patient to profound coma in about 30 minutes. If untreated, death may occur in 1 to 2 hours. With the slower-acting compounds such as barbital and phenobarbital, the depression comes on more slowly and lasts longer; although it is never as profund as that seen with the short-acting barbitures. The following treatment is recommended: (1) Provide adequate airway if tracheal obstruction is present with continuous oxygen and frequent aspiration of secretions. Provide positive pressure oxygen when pulmonary edema is present. (2) Treatment of shock with plasma or whole blood. (3) Give amphetamine in proper dosage and frequency. The dosage schedule for intravenous amphetamine used by the author was 40 mg. of amphetamine intravenously as initial dose, followed by 20 mg. every half hour. It became evident, however, that larger doses could be given safely up to 100 mg. every ½ hour to 1 hour, when careful clinical observation was available. (4) Gastric laveage if the patient had taken the drug within 2 hours of admission. (5) Adequate hydration with intraveous fluids. (6) Penicillin by intramuscular injection. (7) Indwelling urethral catheter. (8) Frequent observation by nursing staff for signs of increaing coma. The author stresses that during the past few years there has been a progressive increase in the number of barbiturate deaths and poisonings.

(H. L. Dick. *Am. J. of the Med. Sci.*, 224:281, 1952.)

Bilateral Carcinoma of the Breast

Statistics reveal an incidence of between 1.96 and 9.90 per cent of bilateral cancer of the breast. The review is based on the material of the Surgical University Hospital in Vienna, Austria, over a period of 50 years. Among 2280 cases of carcinoma of the breast there were 69 bilateral cases or 3.0s per cent. Among these 69 patients 17 showed a history of cancer in the family, in 19 the history was negative, in 33 no history was elicitable. The main incidence rate was found in the age period of 45 to 49. In 19 cases the bilateral tumors occurred within the same year. There was one case of bilateral sarcoma of the breast with an interval of 18 years. Thirteen of the patients were still alive at the time of the report; their age is between 42 and 85. Of the 56 patients who are dead, only 24 could be traced as to their ovarian function at the time of the operation. The life expectancy was 1.83 years in the still menstruating group and 4.41 years in the non-menstruating group. From the observations in both the living and the dead patients the author concludes that ovarian function appear to shorten the life expectancy in cases of bilateral breast cancer. But the number of cases is not large enough to permit a significant statistical result. The author emphasizes that most of the tumors of the second breast were primary tumors as metastatic breast carcinomas are very rare. Skin infiltration between the breasts is a conspicuous sign.

(E. Schmidt, *Langenbeck's Archiv f. klin. Chir. und Deusche Ztschr. J. Chir.*, 272:359, 1952.)

Intra-Arterial Priscoline Therapy

An initial dose of 20 mg. priscoline is used in the leg and of 12½ mg. in the arm. Eleven patients had gangrenee of the heel; 8 healed and 3 had to undergo amputation. 49 had ischemic lesions in other parts of the extremities. In 26 the intraarterial therapy was ineffective. 7 cases of acute arterial occlusion were treated. In 2 amputation had to be dcne. 4 cases of intractable Raynaud's diseases were treated. The attacks disappeared during and for some time after intraarterial priscoline therapy. In 5 cases of functional vascular disturbances, intraarterial priscoline had a temporary and localized vasodilator effect. Priscoline is injected rapidly into the artery. Contraindications are the development of systemic reactions after intraarterial injections of 10 mg. priscoline or less, a temporary decrease in local blood flow in ischemic areas or the development of edema and skin maceration in an ischemic area.
(H. I. Lippmann. *Angiology*, 2:69, 1952.)

Senility

Report of 54 patients who received 300 mgs. of nicotinic acid by mouth and 100 mgs. perenterally per day for a maximum period of three months, gradually reduced to 100 mgs. daily by mouth for an indefinite period. The author concludes that some deficiency in nicotinic acid may be a factor in the etiology of psychosis of senility, and at least one action of niacin would be to replace the deficiency. Niacin may be of more benefit in prophylaxis than in cure. Administration of small daily doses to presenile and senile age groups may prevent or delay the onset of an appreciable number of psychoses of senility.
(Ian Gregory. *Am. J. Psychiat.*, 108:888, 1952.)

A New Antipruritic

This new antiprutitic (N-ethyl-o-crotonotuluide) was used in a series of 200 patients with various forms of pruritic dermatoses with results that were "excellent" (34%), "very gratifying" (31%), "some relief" (22%), and "unaffected" (13%). The medicament was applied in the form of a 10 per cent dilution of the drug, in a vanishing cream base. The period of treatment varied from a few days to several months, according to the severity of the condition. Acute cases in the exudative or vesicular stage were not included, and in most cases of dermatitis venenata the acute stage had passed before application of the cream.

Local reaction to the medicament were minimal. In six instances in which there was objection to the medicament on account of some irritation, patch tests gave only one positive reaction. The detailed results show that in neurodermatoses excellent or good results were obtained in 70 per cent; in eczematoid dermatoses, in 64 per cent; in toxic and allergic erythemas, in 80 per cent; in dermatoses due to living organisms, in 38 per cent; and in a group of miscellaneous dermatoses in 65 per cent.

In 115 instances information was available concerning the action of the medicament compared with other forms of treatment: in 76.6 per cent, there was a report of "more relief than from all other local applications." It is concluded that the new preparation was "found to be an excellent antipruritic, essentially nonirritating except in acute eruptions, without systemic toxicity, and of low sensitizing index."
(J. M. Hitch, *Brit. J. Dermatol.*, 64:408, 1952)

Relapsing Pancreatitis

The treatment is far from satisfactory; none is specific. Medically one tries to institute preventive measures (no alcohol, reduction of overweight, no greasy food, avoidance of stress); provide palliative treatment for acute attacks (opiates, ephedrine, atropine, glucose in case of dehydration, vitamins, amino acids); employ dietary and substitution therapy for certain complications (sequelae such as diabetes mellitus and steatorrhea are treated by diet and replacement therapy, insulin for diabetes and pancreatin for diabetes and pancreatin for streatorrhea) Surgical treatment seems to be more satisfactory than medical management. Surgery is indicated to arrest recurrent attacks; to drain pancreatic abscesses and pseudocysts; to relieve obstruction of duodenum and common bile duct; to remove calcified masses from the pancreas and to relieve pain. Surgical treatment should be avoided during the acute phase, unless an abscess needs drainage.

(E. E. Gambill. *J. of the Kentucky State M. Assoc.*, 6:50, 1952)

in whooping cough

ELIXIR BROMAURATE

GIVES EXCELLENT RESULTS

Cuts short the period of illness and relieves the distressing spasmodic cough. Also valuable in Bronchitis and Bronchial Asthma. In four-ounce original bottles. A teaspoonful every 3 to 4 hours.

GOLD PHARMACAL CO. **NEW YORK CITY**

for Quick Action!

in the Respiratory and Circulatory Emergencies of Intravenous Barbiturate Anesthesia

COUNCIL ACCEPTED

inject **Metrazol**

1 to 3 cc. and repeat intravenously, intramuscularly, subcutaneously

collapse following accidents · surgical trauma opiate and barbiturate depression · asphyxia · denarcotization after general anesthesia ·

Ampules 1 and 3 cc., tablets, solution, powder

Metrazol, brand of pentamethylentetrazol, Trade Mark, reg. U. S. Pat. Off.

BILHUBER-KNOLL CORP. **ORANGE, NEW JERSEY**

NEW PHARMACEUTICAL PRODUCTS

Donnatal Plus: Each tablet contains hyoscyamine sulfate 0.1037 mg., atropine sulfate, 0.0194 mg., hyoscine hydrobromide 0.0065 mg., and phenobarbital 16.2 mg., plus the B complex factors, thiamine hydrochloride 3 mg., riboflavin 2 mg., nicotinamide 10 mg., calcium pantothenate 2 mg., and pyridixine 0.5 mg.

Used in: Treatment of fatigue states associated with abnormal carbohydrate metabolism.

Dosage: Three to nine tablets daily according to clinical response.

A. H. Robins Co., Inc.
Richmond, Virginia

Bicillin, with Sulfose: Each teaspoonful and each tablet contains 150,000 units N,N'-dibenzylethylenediamine dipenicillin G and 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine in a special alimina gel base.

Used in: Treatment of all infections caused by organisms sensitive to the action of penicillin or the sulfonamides.

Dosage: Orally, in varying amounts depending on age.

Wyeth, Inc.
Philadelphia, Pennsylvania

Lusyn: Each tablet contains 5 mg. of homatropine methylbromide, 15 mg. of Phenobarbital, and 300 mg. of alukalin.

Used in: Functional gastrointestinal disorders, intestinal spasm, biliary spasm, pylorospasm, cardiospasm and irritable colon.

Dosage: Adult dosage is one or two tablets before meals.

Maltbie Laboratories, Inc.
Newark 1, New Jersey

Cortisone Acetate: A sterile aqueous suspension of cortisone acetate. Each cc. contains 25 mg. of cortisone acetate in physiologic salt solution with 4 mg. polysorbate 80 and 5 mg. carboxymethylcellulose as suspending agents. Preserved with benzyl alcohol 1.5% w/v.

Used in: Rheumatoid arthritis, acute rheumatic fever and allergic diseases such as asthma, inflammatory eye diseases, and Addison's disease.

Dosage: Administered intramuscularly — average dose 100 mg.

The Upjohn Company
Kalamazoo, Michigan

Bifacton: Tablets containing Vitamin B-12 with intrinsic factor concentrate.

Used in: Treatment of pernicious anemia.

Dosage: As directed.

Organon, Inc.
Orange, New Jersey

Ol-Vitum: Water soluble polyvitamin capsule of supplementary potency, including vitamin B-12, synthetic vitamin A palmitate, vitamin E (Tocopherols).

Used as: Vitamin supplement.

Dosage: Children over 6 and adults, 1 capsule daily.

Ives-Cameron Company
New York 16, New York